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PLATELETS, THROMBOSIS AND VASCULAR DISEASE*

J. F. MUSTARD, M.D., Ph.D.(Cantab.),† *Toronto*

THERE IS no doubt now that platelets play a vital role in physiological blood coagulation, hemostasis and thrombosis. It seems most likely that the platelet and coagulation are intimately associated with each other in their effect on hemostasis and thrombosis. In this report the problem is approached from this point of view, although some workers deny that such a relationship exists. This subject will be discussed in three divisions:

(1) Coagulation *in vitro* in static and dynamic systems.
(2) Coagulation in atherosclerotic and control subjects and the influence of dicumarol and the ingestion of fat on it, and
(3) The possible role of the platelet in early atherogenesis.

COAGULATION *In Vitro*

Native blood or platelet-rich plasma was allowed to clot in a glass tube at 37° C. Serial samples were removed at intervals of a minute or less. The clotting changes were virtually arrested by placing them in silicone-coated tubes containing 3.8% trisodium citrate kept at 4° C. Each sample was subsequently assayed for Factor IX (Christmas Factor, P.T.C.), Factor VIII (A.H.G.), Factor VII (Stable Factor) and Factor V (Labile Factor) activity, and for platelet adhesiveness. The times of onset of platelet clumping and fibrin formation were recorded. Thrombin formation was measured. A detailed account of this work is published elsewhere.[1] The results of one such study are shown in Fig. 1. There is a steady rise in Factor IX activity and platelet adhesiveness, culminating in the clumping of platelets which is followed by a precipitous fall in Factor VIII and Factor V activities. At about this point, the onset of detectable thrombin formation occurs and this is shortly followed by fibrin formation. Factor VII activity shows little change until the point of fibrin formation, then it shows an increase in activity. Coagulation, if viewed in this way, can be divided into three stages: stage one, the period between the onset of coagulation and the onset of platelet clumping, hereinafter referred to as "the early stages of coagulation"; stage two, the interval between the onset of platelet clumping and fibrin formation; and stage three, events following the formation of the fibrin clot.

The changes in the various clotting factors, shown here, are similar to those reported by others. Johnston and associates[2] have reported that Factor VII activity increases after the blood clots. Hougie,[3] in a detailed study of the changes which occur during the clotting of normal and pathological blood, reported that Factor VII activity increases after the formation of the fibrin clot. This evidence indicates that there is an increase in Factor VII activity during blood coagulation, but that this change occurs mainly in the later stages. Factor VIII and Factor V activities disappear mainly during the second stage of coagulation, between the onset of platelet clumping and fibrin formation. Factor IX activity and platelet adhesiveness increase during the early phase before there is any morphological change. White, Aggeler and Glendening[4] and Lewis *et al.*[5] have also reported that Factor IX activity increases during coagulation. Surgenor, Steele and Wallach[6] have reported that platelets are involved in the activation of Factor IX, and Seegers and Johnson,[7] that these particles are involved in the formation of autoprothrombin II (probably Factor IX). The present findings indicate that there is a parallel between changes in platelet adhesiveness and Factor IX activity. The exact nature of this association is unknown at present.

Knowledge of the changes in clotting factors during coagulation is valuable when one is designing studies to investigate the nature of clotting *in vivo*. Whole blood clotting times (if these can be done accurately) should reflect the overall nature of the clotting mechanism. However, this test, as it is usually performed, is technically unsatisfactory and provides no specific information about the early stages of clotting. If one believes the clotting process is a series of reactions with checks at each stage, it is conceivable there are differences in the

*From the Department of Medicine, University of Toronto, Sunnybrook Hospital, Department of Veterans Affairs, Toronto and Department of Physiological Sciences, Ontario Veterinary College, Guelph. Presented at a meeting of the New York Society for the Study of Blood, New York, November 16, 1960.
†Senior Research Associate, National Heart Foundation of Canada.

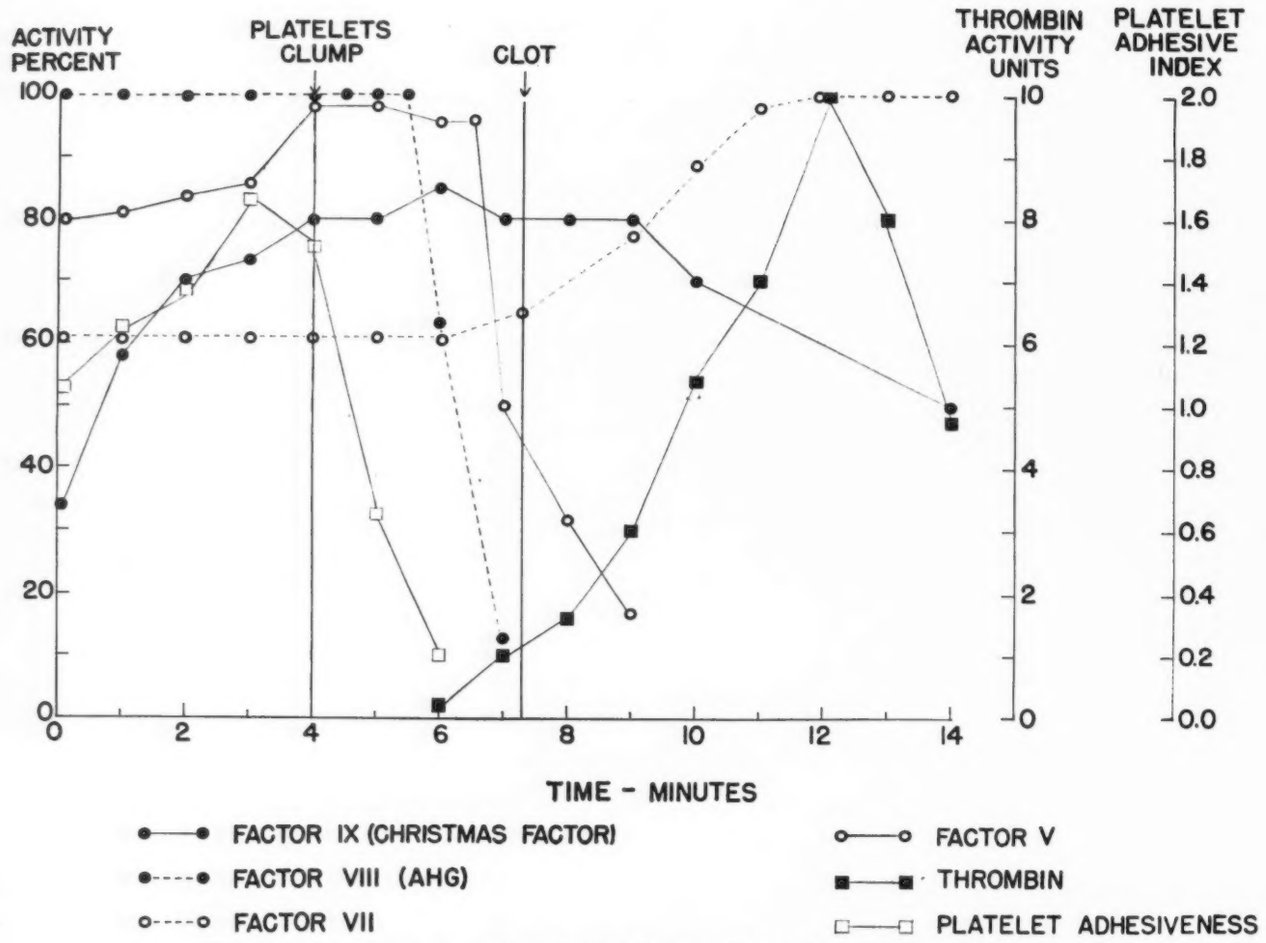

Fig. 1.—The change in various clotting factors during the coagulation of blood in a glass tube at 37° C. Factor IX, Factor VIII, Factor VII and Factor V are expressed as per cent activity.

early stages which are damped out and therefore not recognized in less specific tests. However, such differences would be important only if they produced morphological changes, that is, platelet clumping or fibrin formation and/or changes in viscosity.

Despite the original work of Bizzozero[8] and Eberth and Schimmelbusch,[9] the more recent work of H. D. Zucker,[10] Marjorie Zucker[11] and Fulton, Akers and Lutz,[12] many people believe that an intravascular clot is composed mainly of fibrin; for example, Duguid,[13] who proposes that thrombi are important in the development of atherosclerosis, ignores platelets. Many investigators have studied tissue thromboplastin concentrations in the intima of vessels on the hypothesis that excessive concentrations might lead to fibrin formation.[14] The work of Bizzozero[8] showed that if the lining of a vessel is damaged, a reticulum of clumped platelets is formed, with some red and white cells trapped in the interstices of it; such a thrombus consists primarily of platelets. The vessel injury produced in Fulton's[12] experiments on the microcirculation certainly does not lead to obvious fibrin deposits but to platelet thrombi. Furthermore, when the endothelium is scraped from the surface of a rabbit's aorta, the material which accumulates is composed of platelets and white cells.[15] This is true even in veins where the flow is sluggish.[16] Thus, there seems little justification for the view that intravascular thrombi, formed following endothelium damage, are initially composed mainly of fibrin. The primary material found is a white thrombus of platelets and white cells, with fibrin as a secondary feature. Because of the presence of plasma on the surface of the platelet, trace amounts of fibrin are probably present in the early platelet clumps.

The formation of thrombi in high-flow pulsatile systems can be studied readily in extracorporeal shunts.[17] Plastic or brass models of various vessel configurations were coupled into the circulation of living swine. The duration of such experiments is 20 minutes on the average, with a rate of flow that varies between 300 and 700 ml. per minute. Fig. 2 shows a typical arrangement; one catheter has been inserted into the carotid artery, the other into the contralateral jugular vein. All surfaces in contact with the blood were silicone-coated. In such a system deposits, ranging in size from microscopic platelet thrombi to extensive mixed red clots, were almost always formed. Platelets are the earliest and the only invariable constituent. They have been identified by histochemistry; other morphological confirmation was obtained by electron microscopy

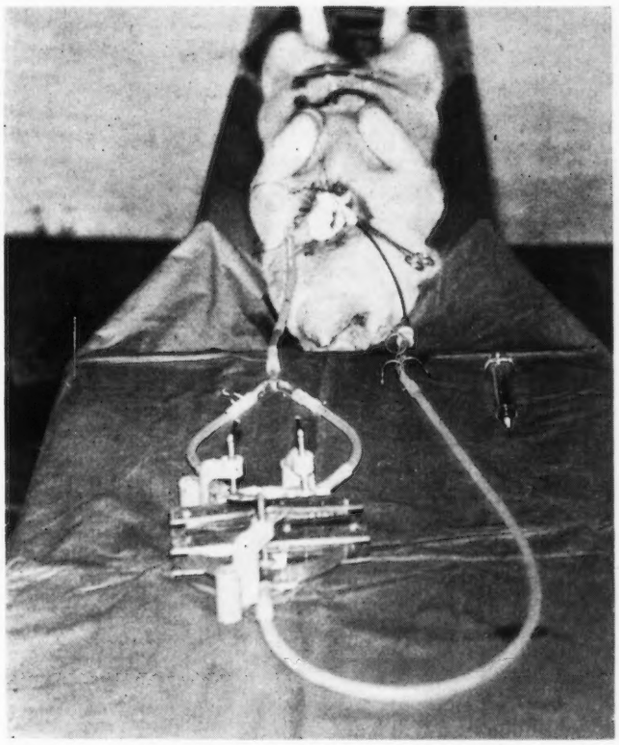

Fig. 2.—A photograph of a flow chamber coupled into the circulation of a living pig. The tube on the right is inserted into the carotid artery and that on the left into the jugular vein.

and by fluorescent antibody techniques, and further proof was obtained by radioisotope studies.[17]

Thus the morphological sequence seen when blood clots in a glass tube is also observed when thrombi form from flowing blood; first there are platelets and a few white cells with traces of fibrin and in time, if conditions are favourable, extensive fibrin deposits occur.

These studies, which are similar in scope to those reported by Shionoya[18] and Best, Cowan and MacLean,[19] confirm and amplify their findings. The work of Poole,[20] using an *in vitro* system entirely, leads to similar conclusions. It should be possible to prevent the formation of platelet thrombi by the administration of drugs which inhibit the early stages of coagulation on which the process is dependent. Figs. 3a and 3b show a flow chamber model of an aneurysm. In Fig. 3a, a study on a control pig, there is an extensive mixed clot after 20 minutes' perfusion. In Fig. 3b, on a pig which was given 15,000 units of heparin intravenously 10 minutes before the start of an experiment, there is no gross microscopic evidence of thrombus formation after the same period of time.

Dicumarol administration also influences the amount of thrombus formed in these experiments. Fig. 4a shows the result of a perfusion experiment in which the pig was given sufficient dicumarol to prolong the prothrombin time to 40 seconds; Fig. 4b shows the result when the prothrombin time was prolonged to 18 seconds only (normal value 14 seconds). In the latter experiment, there is a heavy deposit far in excess of that seen in animals not receiving anticoagulants. In the experiment shown on the left, Fig. 4a, there is minimum evidence of thrombus formation. The results of another experiment indicate that slight prolongation of the prothrombin time leads to increased thrombus formation in this type of study.[21] This is similar to the findings reported by Fulton, Akers and Lutz[12] on artificially induced thrombosis in hamsters receiving dicumarol. Horlick[22] reported that small doses of dicumarol tend to increase platelet adhesiveness in man. These are disturbing observations because they indicate that, although dicumarol and related drugs can produce an antithrombotic effect, they have no anticoagulant effect in the lower ranges and may have the very opposite effect.

Adequate doses of heparin and dicumarol decrease platelet adhesiveness and delay the time of onset of platelet clumping.[21] In those experiments in which thrombus formation has been prevented, these drugs were administered in doses which caused decreased platelet adhesiveness and delayed platelet clumping. Therefore, it is reasonable to conclude that drugs which influence the early stages of clotting interfere with platelet function and prevent thrombus formation.

COAGULATION IN ATHEROSCLEROTIC AND CONTROL SUBJECTS

The evidence presented in the first part of this paper indicated that the most fruitful area in which to search for significant differences is that part of clotting up to, and including, the clumping of platelets.

Available evidence suggests that there may be important changes in the early stages. In 1957, McDonald[23] reported that, on the average, subjects with clinical coronary artery disease generate more

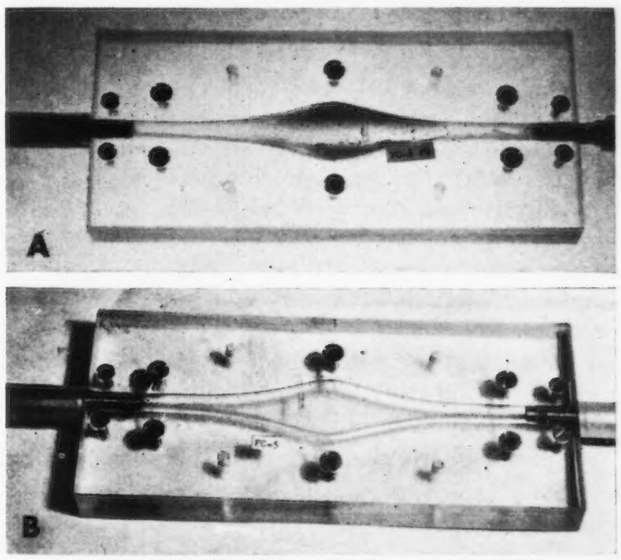

Fig. 3A.—Aneurysm flow chamber after 20 minutes of blood flow in a shunt coupled into a normal pig. The chamber has been freed from the shunt and rinsed with saline. The area where the main stream passes is relatively free of deposit, but the expansion heavily coated. Flow is from right to left.

Fig. 3B.—The same flow chamber after 20 minutes of blood flow in a shunt coupled into a pig which was given 15,000 units of heparin 10 minutes before the experiment.

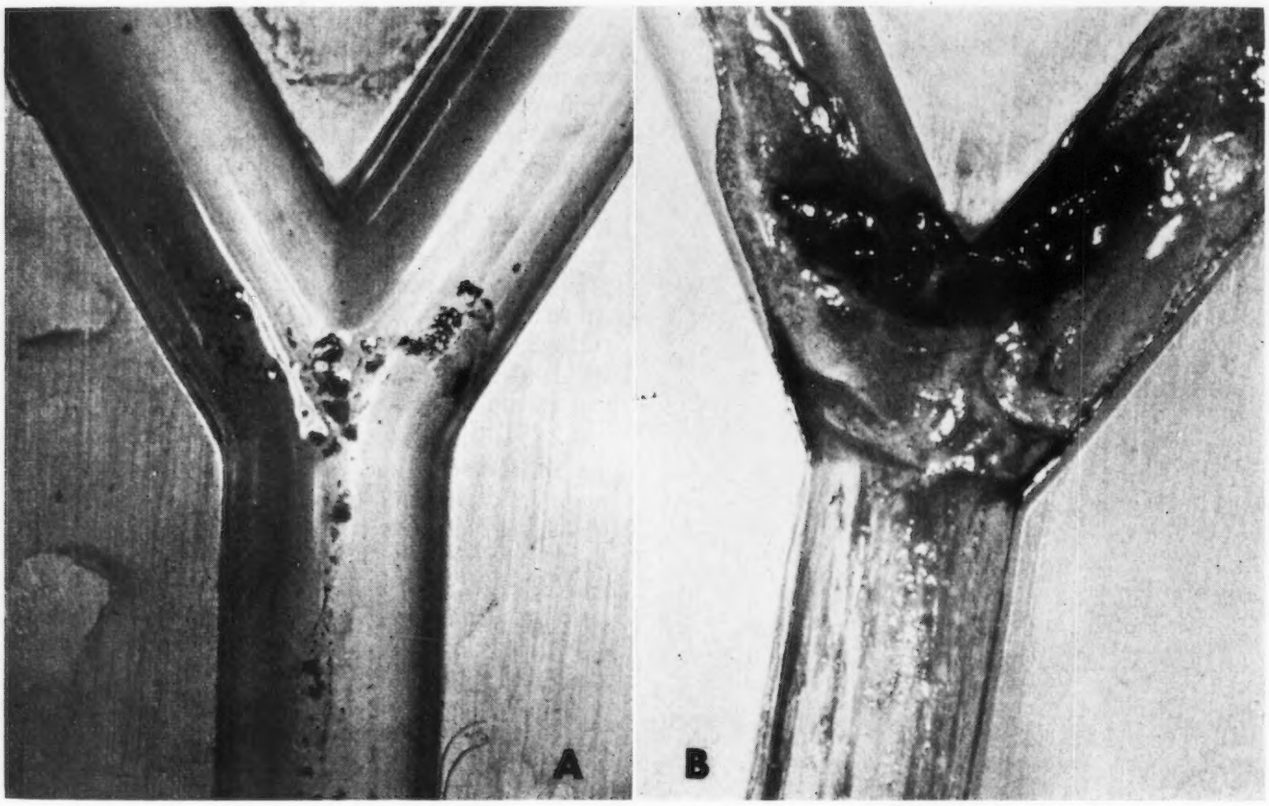

Fig. 4A.—The deposit in a bifurcation flow chamber after a 20-minute perfusion with blood from a pig receiving dicumarol and with a prothrombin time of 40 seconds.
Fig. 4B.—A similar experiment in a pig receiving dicumarol, but with a prothrombin time of 18 seconds (normal 14 seconds). The deposit is much heavier in this experiment.

thromboplastin and have platelets which exhibit a greater degree of adhesiveness than those in control subjects. We also reported a difference in thromboplastin generation thought to be the result of plasma Factor IX activity.[24] Recently, Spittel and associates[25] reported a significant difference in coagulation, as measured in a modified thromboplastin generation test, between patients with and without a history of arterial or venous thrombosis. They concluded that the factor responsible for the difference was not a clotting factor, currently recognized, but one active in the early stages of coagulation. Horlick[22] has confirmed the differences noted by McDonald between platelet adhesiveness in control and coronary subjects. However, Merskey *et al.*[26] were unable to find any clearly defined differences using tests which reflect mainly the later stages of clotting. The only test used by these workers, which may measure the early stages, was an unmodified form of the thromboplastin generation test which did not show any definite differences. Although most of the evidence in the literature suggests that there may be differences in the early stages of clotting, between subjects with clinical evidence of atherosclerosis and controls, studies of this nature are open to the criticism that the *in vitro* tests may not reflect accurately the *in vivo* state of the coagulation mechanism. Since platelets are expended in the early stages of clotting, the measurement of platelet survival and turnover can be regarded as an *in vivo* index of the activity at this stage. Certainly no better measure is available at present.

Recently, we have completed a study of clotting in atherosclerotic subjects and controls by *in vitro* and *in vivo* tests,[27] in which 75 male subjects were studied. Thirty-one had clinical evidence of some complication of atherosclerosis such as myocardial infarction, angina pectoris, carotid or basilar artery stenosis or occlusion, or intermittent claudication. None of these subjects had an acute occlusive episode during the three months preceding the present study, nor were any of them on dietary or anticoagulant therapy. The control group was drawn from normal healthy subjects and from patients with a variety of conditions believed to be unrelated to atherosclerosis (e.g., prolapsed intervertebral disc disease, psoriasis, neurodermatitis and chronic bronchitis). No patients with cancer, collagen disease, diabetes, gout or venous thrombosis were used as controls. The following *in vitro* tests of coagulation were carried out: whole blood clotting time, prothrombin time, platelet count, platelet adhesive index, platelet clumping time and plasma thromboplastin time (that is, the activity of dilute plasma, used instead of serum, in the thromboplastin generation test). Each test was performed five times on each subject and from these an average value was computed for each. Platelet survival was estimated by the use of diisopropyl fluorophosphonate, the phosphorus of which was in the form of P^{32}, according to the method of Leeksma and Cohen.[28]

The evaluation of platelet survival is difficult since the true pattern of platelet destruction is unknown. Survival may be dictated by a normally distributed life span and, if all the circulating platelets have an equal chance of being labelled, the distribution should follow the second integral of the normal Gaussian or linear curve which tends to zero. If the distribution is random the curve of destruction would be exponential and identical, whatever population is labelled. Finally, the pattern of destruction may be a compound of these two forms or may be described by some other mathematical function. In this study, we have used two mathematical treatments, (1) exponential and (2) Gaussian or linear.

A plot of the Gaussian mean against the exponential mean in 161 miscellaneous subjects gives a correlation coefficient of +0.872. These values provide evidence that, while the two methods give different results, they are correlated closely and both probably provide good indices of true mean platelet survival.

The *in vitro* clotting tests showed no significant differences between the mean values for the clotting time, the prothrombin time, the platelet clumping time or the platelet count. The platelet adhesive index has an experimental error of 30%, although in this study this error is reduced because of the multiple readings in each subject. Despite the technical error, there was a highly significant difference between the mean platelet adhesive index values for the two groups, the atherosclerotic group having platelets with greater adhesiveness. There was also a highly significant difference between the mean values for the plasma thromboplastin time of each group.

No doubt the control group contains some subjects with advanced atherosclerosis which was not manifested clinically. Furthermore, some of the subjects in the atherosclerotic group will have had incorrect diagnoses.[1] If the atherosclerotic group contains only those with a positive family history of the complications of atherosclerotic vascular disease and the control group only those with a negative family history, it is possible that the extent of misclassification will be reduced. When this was done, the differences between the mean values were enhanced without exception. The control group with a positive family history and the atherosclerotic group with a negative family history were similar to each other and intermediate between the other two groups.

The results for the platelet survival studies were similar to the results of the platelet adhesive index.[27] Comparison of the mean platelet half-life values for the atherosclerotic and control subjects show a significant difference which was reflected to a lesser degree in the mean platelet turnover values. The atherosclerotic subjects had a shorter mean platelet half-life and greater platelet turnover than the controls. As with the *in vitro* clotting tests, the differences are enhanced if the control group with the negative family history is compared with the atherosclerotic group with a positive family history. The differences found, between atherosclerotic and control subjects, by *in vitro* tests of the early stages of clotting are confirmed by the results of the *in vivo* estimates of platelet half-life and turnover.

In view of the chronological relationship between the clotting factors, discussed at the beginning of this paper, the statistical interrelationships for the data from the present study have been evaluated. It may be said, in general, that plasma thromboplastin activity (Factor IX activity) and measurements which involve the platelets are related to one another, but are poorly related to those tests which measure the later stages of coagulation.

In the relationship of these tests to the evaluation of platelet survival and turnover, the most impressive and uniform correlations are found with the platelet adhesive index (Tables I and II). Both Factor IX activity and the platelet clumping time show fairly good correlation.

TABLE I.—CORRELATION BETWEEN IN VITRO COAGULATION TESTS AND PLATELET TURNOVER IN ATHEROSCLEROTIC AND CONTROL SUBJECTS
(75 Readings)

Correlation between platelet turnover and	*Correlation coefficient r*	*p Value*
Whole blood clotting time.....	−0.12	>0.05
Prothrombin time.....	−0.23	<0.05*
Platelet clumping time.....	−0.45	<0.001***
Plasma thromboplastin time... (Factor IX)	+0.48	<0.001***
Platelet adhesive index.....	+0.58	<0.001***

TABLE II.—CORRELATION BETWEEN IN VITRO COAGULATION TESTS AND PLATELET TURNOVER IN ATHEROSCLEROTIC SUBJECTS RECEIVING DICUMAROL
(54 Readings)

Correlation between platelet turnover and	*Correlation coefficient r*	*p Value*
Whole blood clotting time.....	+0.07	<1.0
Platelet clumping time.....	−0.14	<0.3
Prothrombin time.....	−0.23	<0.1
Plasma thromboplastin time...	+0.48	<0.001***
Platelet adhesive index.....	+0.54	<0.001***

These findings become more impressive when it is recalled that all these tests, *in vitro* and *in vivo*, are subject to a very large experimental error. It must be emphasized that both in correlation and in comparison of means, if the collection and analysis of the data have been unbiased, experimental error tends to an underestimate of the significance of the results only. Although these clotting tests and studies of platelet survival seem to be more sensitive than other older tests, they still have grave deficiencies, and a more accurate method of evaluating platelet adhesiveness would be a valuable addition to present methods. On the other hand, though the results presented show differ-

ences for *mean* values between the various groups, they provide no information about the overlap of the respective distribution curves and hence about the discriminant value of the tests. The percentage misclassifications using all the data available in the most efficient manner is 20% (i.e., only two-and-one-half times as efficient as random guessing), which is too high to give these measures any diagnostic value at present.

The net results indicate that there are differences in coagulation between atherosclerotic and control subjects and that these differences probably exist during the early stages of clotting. While the evidence shows that the economy of the platelet has a role in the complications of atherosclerosis, the nature of the relationship is not clear. Advanced atheroma with intimal ulceration may encourage platelet deposition and, by increasing the rate at which they are consumed, may activate Factor IX, possibly by mechanisms already discussed. However, these changes in platelet activity may have existed from an early age and may have been a factor in the development of encrustations and atherosclerosis. Only extensive study can answer these questions.

In view of the close relationship between the *in vivo* turnover of platelets and tests of the early stages of clotting, the following questions arise: whether the platelet turnover causes the changes in clotting; whether the clotting activity influences platelet turnover; or whether they are independently related to a common factor. If the activity of the clotting mechanism influences platelet turnover, then, from the flow chamber studies, the administration of adequate amounts of heparin or dicumarol would be expected to prolong platelet survival time and decrease platelet turnover.

Twenty-nine male subjects suffering from clinical complications of atherosclerosis were given dicumarol, in doses sufficient to decrease platelet adhesiveness and prolong platelet clumping, and platelet survival studies were done. The results showed that platelet survival was significantly longer and platelet turnover significantly less in the atherosclerotic subjects receiving dicumarol.[29] Since the mean platelet counts were similar, this response indicates that subjects receiving dicumarol are producing and using fewer platelets than the untreated group. Furthermore, the evidence suggests that changes in clotting have an influence on platelet survival and turnover. However, whether the fate of circulating platelets is determined by the external or internal economy of the platelet is unknown. Although it seems reasonable to attribute these results to the lesser demands of the external economy (in this case blood clotting), it is not impossible that dicumarol influences some aspect of the internal economy of the platelet, which in turn influences the activity of clotting.

To study this matter further, coagulation studies were carried out in a group of patients receiving smaller doses of dicumarol.[30] Although these subjects showed some prolongation in prothrombin time, there was no significant change in platelet adhesiveness or platelet clumping. These subjects did not show any significant difference in platelet survival or turnover from the atherosclerotic subjects. Twelve of these 22 subjects have had these studies repeated during treatment with dicumarol in an amount sufficient to delay platelet clumping and decrease platelet adhesiveness. When this was done, these subjects had a significantly prolonged platelet survival time and decreased platelet turnover. These findings provide further evidence that the effect of adequate doses of dicumarol on platelet survival is mediated through changes in the external economy of the platelet, in this case the blood clotting mechanism. This seems reasonable in view of the evidence that stimulation of the clotting mechanism by the administration of suitable agents produces a precipitous fall in circulating platelets.[31, 32]

The fate of the platelet is still unknown, but, without doubt, *not* determined by a single factor. However, the close relationship between the measurement of platelet adhesiveness and that of turnover suggests that the adhesiveness of platelets is a contributory factor in their destruction. This is a point of considerable theoretical importance. If the widely held view that platelet survival is normally distributed about a mean is correct, then either adhesiveness increases with the age of the platelet or it has little to do with platelet survival. On the first point, the scanty evidence available from the work of Helen Payling Wright[33] suggests that, if anything, the *younger* platelets are the more adhesive. On the second point, apart from the probability that the more adhesive platelets are likely to be used first in maintaining the integrity of the vascular tree, administration of adequate dicumarol causes both prolongation of platelet survival and reduction in platelet adhesiveness. Furthermore, studies using heparin have shown an effect similar to that achieved with adequate doses of dicumarol.[34] Platelet destruction probably follows some pattern other than linear, at least in atherosclerotic subjects.

Another question of considerable importance is whether there is normally a continuous *in vivo* process, short of frank clot formation, which involves the consumption of clotting factors. If this is so, the turnover of clotting factors will be diminished by anticoagulants. Hasselbach and Hjort[35] could not find any evidence of this diminution, using techniques which measure the middle stages of coagulation. Lewis[36] found that the turnover of fibrinogen in dogs was not modified by the exhibition of coumadin. Two doubts arise about such studies, however: firstly, the dose of anticoagulant may have been insufficient to influence *in vivo* clotting, and secondly, the changes may be located primarily in the early stages of clotting. Certainly, the evidence from our studies on the

effects of adequate doses of dicumarol and heparin in atherosclerotic subjects suggests that there may be a small amount of continuous *in vivo* coagulation. However, the evidence is open to other interpretations and, therefore, does not provide a final answer to the question.

During the past decade, there has been much interest in the relationship between alimentary lipemia and blood coagulation. Despite numerous reports, there is no clear-cut evidence that the ingestion of fat significantly influences clotting *in vivo*. Duncan and Waldron[37] first reported that the ingestion of cream shortened the whole blood clotting time. Fullerton, Davie and Anastasopoulos[38] found that this was also true in Europeans. However, at about this time, Tulloch, Overman and Wright[39] published the first of the negative series entitled "Failure of Ingestion of Cream to Affect Blood Coagulation". Analysis shows, however, that there is a highly significant shortening of the clotting time after the ingestion of dairy fat (Table III). Clotting tests are difficult to perform accurately, and the indefinite nature of the end point leads to bias which Merskey and Nossel[40] have so clearly shown. Accordingly, the data of Tulloch, Overman and Wright[39] provide more convincing evidence that the ingestion of dairy fats does shorten the clotting time *in vivo*, since if the study was biased, it was biased against lipemia affecting blood coagulation. A subsequent paper by this group[41] did not show any significant change, however, Manning and Walford[42] and Merskey and Nossel,[40] in an extensive study, were unable to find any significant shortening of the whole blood clotting times following a fatty meal. (During this discussion, the effect of lipemia on the Russell's viper venom time is being ignored.) Buzina and Keys[43] and others[44-47] reported that the clotting time of blood and plasma is shortened during lipemia. Sheehy and Eichelberger,[48] using the thrombelastograph and siliconed clotting times, could not demonstrate any effect. However, comparison of the mean differences for the clotting times of their subjects, after meals rich in olive oil or dairy fats, shows that there is actually a significant difference for this part of their study (Table IV). This may simply mean that the meal of olive oil tended to prolong the clotting time. Nitzberg *et al.*[49] could not find any definite evidence of an effect of alimentary lipemia on blood clotting times. However, examination of their data, for the thrombelastograph, shows that there is a highly significant shortening of the r value during lipemia (Table V). (The r value in this instrument is roughly equivalent to the clotting time.) In view of the objective nature of this test and the highly significant difference, we cannot accept the conclusion of the authors that the ingestion of fat does not shorten the clotting time as measured on the thrombelastograph.

Three points need to be emphasized: The first of these is that clotting times are extremely variable, and examination of data which does not apply efficient analysis can lead to false negative results. Thus, three of the studies[39, 48, 49] frequently quoted in the literature as negative, actually show that the ingestion of fat influences the clotting time of blood. The second point is that the clotting time is usually an insensitive test of changes in clotting which may (if they occur) be very slight and confined to only one phase of coagulation. Thirdly, failure to recognize that individuals do not constitute one homogeneous class may lead to the obscuration of differences in one class by the absence of difference in the other.

All the evidence available indicates that lipids primarily influence the early stages of clotting. The work of Surgenor's group[6] and of Seegers and Johnson[7] suggests that phospholipids may play a role in the activation of Factor IX. There have been very few studies of the effect of fat ingestion on the early stages of clotting. Over ten years ago

TABLE III.—MEAN CHANGE IN WHOLE BLOOD CLOTTING TIME 1, 2 AND 3 HOURS AFTER A MEAL RICH IN CREAM[39*]

Time	*1 Hour*	*2 Hours*	*3 Hours*
Mean change in whole blood clotting time minutes	−3.1	−5.7	−4.3
(Paired differences) p	<0.01**	<0.001***	<0.001***

*Based on data for blood taken into new syringes.

TABLE IV.—COMPARISON OF THE EFFECT OF MEALS RICH IN CREAM OR OLIVE OIL ON THE WHOLE BLOOD CLOTTING TIME[48]

	Meal	
	Cream 10 subjects	*Olive oil 10 subjects*
Mean change in clotting time minutes Mean of 2 fasting values— Mean of values 1 and 4 hours post-prandial	−1.51	+2.52
Significance of difference in each group		
t	1.529	1.542
p	<0.20	<0.20
Significance of difference between mean change in clotting time for the cream and olive oil groups	t = 2.111 p = <0.05*	

TABLE V.—SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN FASTING AND LIPEMIC R THROMBELASTOGRAPH VALUES[49]

Group	*No.*	*Mean change in r value*	*Paired differences*	
			t value	*p*
Hyperlipemic	8	−0.35	1.767	<0.2
Hypercholesterolemia	10	−1.88	3.085	<0.02*
Normal controls	10	−0.54	3.033	<0.02*
Pooled	28	−0.97	3.687	<0.001***

Moolten and his associates[50] reported that lipemia increased platelet adhesiveness. This was subsequently confirmed by Cullen and Swank[51] in hamsters, and by Horlick[22] in man, while MacDonald and Edgill[52] showed that a diet low in fat had the opposite effect. Recently, both Shimamoto[53] and Goldstein[54] have reported that alimentary lipemia decreases the circulating platelet count. In some subjects, our studies showed an apparent increase in Factor IX activity during lipemia which may have tended to be associated with a decrease in the circulating platelet count.[55, 56] All of the tests used, however, are *in vitro* assays and therefore are open to the criticism that the changes are artefacts and do not reflect true *in vivo* effects. The argument could be partly resolved by determining the effects of various types of diets on the turnover of clotting factors such as platelets. We have such studies in progress.

THE POSSIBLE ROLE OF PLATELETS IN EARLY ATHEROSCLEROSIS

One factor which has provided an incentive to studies of the role of coagulation and platelets in vascular disease has been the hypothesis that thrombi are a factor in the development of atherosclerotic lesions. There is now no doubt that thrombi can and do contribute to thickening of the arterial wall.[57-59] The question which remains unanswered is at what stage thrombi begin to play a role. In these studies, it is difficult to distinguish which changes are primordial and which are complications. It is evident from the accepted definition of atheroma, which refers to an advanced and complex change, that the earlier the stage studied the less likely the process is to be generally accepted as true incipient atherosclerosis. Nevertheless, there is some indirect evidence to suggest that intimal thickening and fatty streaks therein are among the earliest recognizable changes.

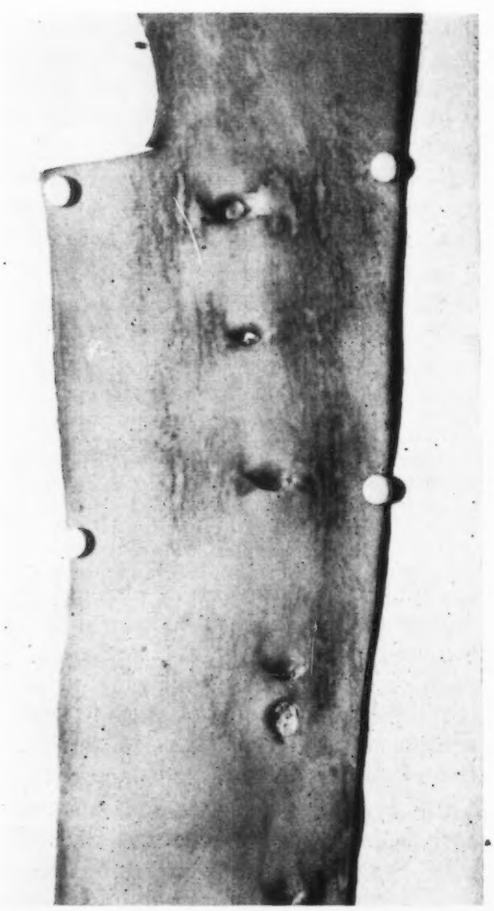

Fig. 5.—The pattern of development of atherosclerosis about the intercostal vessel orifices in a pig. The aorta has been stained with Sudan IV. Note the butterfly-shaped pattern which is beginning to coalesce into the ladder-like pattern.

In investigating whether the encrustation hypothesis explains the early lesions in atherosclerosis, we have been faced with the question: what determines the localization and the character of the lesion? In order to study this problem, a series of experiments were set up using the extracorporeal shunts referred to in an earlier part of this paper. The deposits which invariably formed in the chambers were compared with early lesions of atherosclerosis in respect of their topography, pattern and histochemistry. These comparisons are dealt with in detail in another paper.[60]

At bifurcations, lesions or deposits occur on the lateral aspects of the distributory channels, sparing the parent trunk. The deposit of platelets, red cells and fibrin at a flow chamber bifurcation is shown in Fig. 4a.

About the intercostal vessel orifices, deposits tend to occur laterally and to some extent downstream. As they progress they extend laterally, producing a butterfly-shaped pattern. Several such forms, established at adjacent vessel orifices, may coalesce into a ladder-like pattern. This is illustrated in Fig 5.

Fig. 6 shows a close-up of a pattern about an intercostal orifice in a pig aorta, and Fig. 7, the deposits in an analogous flow chamber model. The parabolic area, spared on the proximal side of the orifice in both cases, with the butterfly-shaped lateral extension, is remarkable. The deposits in the flow chamber exhibit fine curved streaks on the proximal side which suggests the lines of flow and perhaps provides a clue to the mechanism of production of this remarkably constant configuration. On a curve, the deposits tend to be heaviest on the lesser curvature. The early lesions are fine and floccular in pattern, and in the unstained state are semi-translucent. Early deposits in a flow chamber show a fine stippled pattern.

More advanced atherosclerotic lesions coalesce and may produce longitudinal streaks, but there is commonly a transverse barring similar to the ripple marks seen in the sand on a wave-washed beach. This is also seen in the more advanced deposits formed in the flow chamber. This may be due to the pulsatile nature of blood flow in arteries.

As was mentioned in the early parts of this paper, platelets are the earliest and only invariable constituent detectable in these deposits.

Fig. 6.—Close-up view of an intercostal orifice in a pig's aorta showing the sparing of the proximal lip, the curved pattern extending laterally to form floccular linear deposits. This aorta was also stained with Sudan IV.

Most early atherosclerotic lesions take fat stains; in flow chamber deposits, fat staining material, usually visible to the naked eye, was always present. This appears to be intimately related to platelet material.

In consequence, it is of some interest to consider what relationship exists between the cholesterol content of human serum and that of washed platelets. Examination of this relationship in 30 human subjects showed a significant correlation ($+0.64$, $p < 0.01$). A similar but less marked relationship was found between serum and platelet phospholipid values.

The evidence suggests that there is a close similarity between the deposits in flow chambers in a high-flow pulsatile system and the deposits in early atherosclerosis. This is true of the sites of predilection, of the precise topography, of the character of the deposits, and the histochemistry. Thus hydraulic factors, and the physiology of the blood, may explain many facts about early atherosclerosis without invoking the vital properties of the vessel wall.

It can be argued that encrustations may be an early, if not actually a prime, mechanism in atherogenesis, and investigation of this must logically lead to a greater interest in the role of the platelet. This has been discussed in more detail elsewhere.[61]

Of some interest in this regard is the work of Shimamoto,[53,62] who has recently reported that inhalation of cigarette smoke, the administration of adrenaline or feeding of meals rich in fats to rabbits causes the platelets to adhere to the endothelium. He believes that these factors damage the "silicone-like properties" of the endothelium. Certainly, there is no doubt that, under certain conditions, lipemia will lead to fat accumulation in the endothelial cells. The work of Shimamoto suggests that when this does occur, there is a change in the physical property of the endothelium. It may prove very difficult to dissociate the lipid imbibition and encrustation aspects of atherogenesis.

SUMMARY

Studies *in vitro* have shown that extensive chemical and physical changes precede the morphological phenomena of coagulation and that platelets clump before extensive fibrin formation occurs. A similar pattern is seen *in vivo* with flowing blood where platelet deposits form before there is any significant fibrin formation. It is clear then that abnormalities may exist in these stages without frank thrombosis. These facts seem to have been neglected.

The failure of many investigators to find differences in coagulation between atherosclerotic and control subjects may be attributable in part to the non-specific character of the tests which they have employed; tests which measure mainly the later stages of coagulation. Moreover, much of the data suggests, both *in vitro* and *in vivo*, that the activity of the early stages of coagulation is increased in atherosclerotic subjects and that this may be damped down by the use of dicumarol and heparin in adequate doses. Whether environmental factors, such as lipid-rich meals, can aggravate this tendency is still an open question in our opinion.

These differences may be important in the production of atherosclerosis, not only the late, but also the earliest stages. There is some evidence from flow chamber work that platelet deposits may be a prime mechanism in atherogenesis. Since these studies have shown that the lipid associated with platelets reflects that of the serum, this source, together with the lipid from the plasma, which is trapped in the interstices

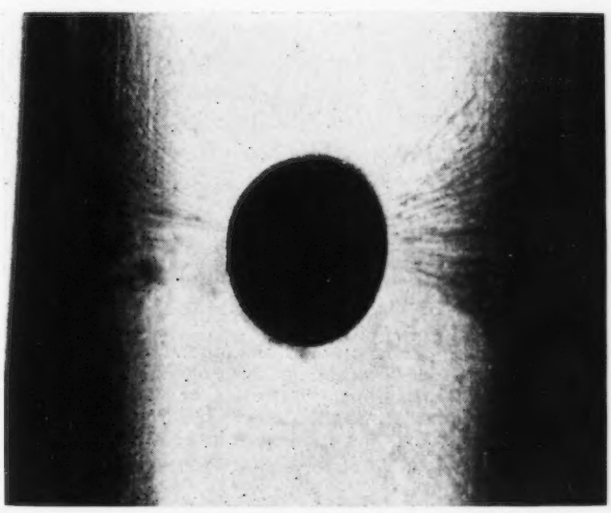

Fig. 7.—The deposit formed in a flow chamber model of an intercostal vessel orifice. The proximal lip is spared with a curved pattern extending out to the heavier lateral deposits. The fine curved streaks of the lateral deposit suggest that hydraulic factors are responsible for this characteristic pattern.

of clumped platelets, may allow a syneresis between the encrustation and lipid theories of atherogenesis, which are commonly regarded as rivals. Lipid changes may participate in other ways, such as by their effects on platelet adhesiveness and on the vital properties of the vascular endothelium.

It seems probable that the development of atherosclerosis is dependent upon the interaction of at least four primary components: the vessel wall, hydraulics of the vascular system, lipids, and encrustations. To emphasize the possible importance of the platelet is not to deny the role of the other factors but it is clear that, once any abnormality has occurred, several other mechanisms such as intimal hemorrhage and calcification may appear and dominate the picture.

Before investigating the hypothesis that platelet deposits are important trigger mechanisms in atherogenesis, there is a fundamental need to determine whether or not platelets are in fact deposited *in vivo* on normal endothelium and, if so, how far the pattern of their deposition is determined by hydraulic factors. In addition, it is important to study the relationship between factors which damage the vessel wall and the formation of encrustations.

The experimental work referred to in this paper was carried out in collaboration with my colleagues, Dr. H. G. Downie, Dr. G. A. Robinson and Dr. H. C. Rosell, Ontario Veterinary College, Guelph, Dr. A. Little, Sunnybrook Hospital, Toronto, and Dr. E. A. Murphy, Department of Medicine, Johns Hopkins Hospital, Baltimore. I am grateful to them for their help in the preparation of this manuscript and for their permission to refer to unpublished work.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

CANCER OF THE STOMACH

All observers are now practically agreed that the chemical examination of the contents of the stomach is not of much value in diagnosis, but the results of repeated analyses may afford important confirmation of the malignity of the condition. Examination of the gastric contents in the early stages means nothing, and the presence of the Oppler-Boas bacillus indicates simply stagnation of food within the stomach and its fermentative destruction. The characteristic result in cancer is absence of free hydrochloric acid, diminished total acidity, and the presence of lactic acid and of the Oppler-Boas bacillus. In a few cases, however, free hydrochloric acid is normal in amount, and its absence and the presence of lactic acid are not specific. On the other hand, an increased hydrochloric acid content is fairly conclusive for ulcer, and a positive finding as regards lactic acid does not negative it. Boas, however, considers this presence of lactic acid as pathognomonic of carcinoma.

A normal content of hydrochloric acid is especially likely to be present if the cancer is developing upon an ulcer. Hertz emphasizes the importance of occult blood in the stools, as minute haemorrhages are constantly occurring from the surface of every malignant ulcer. The best tests for ascertaining this are the guaiacum and benzidene reactions, made with ethereal extracts of stools after treatment by glacial acetic acid. In two hundred and sixty-six cases in which these tests were applied 99 per cent. gave a positive reaction.—Herbert A. Bruce, *Canad. M. A. J.*, 1: 805, 1911.

SPIRONOLACTONE (ALDACTONE) THERAPY FOR ASCITES DUE TO CIRRHOSIS OF THE LIVER*

CHARLES H. LOCKWOOD, M.D., F.R.C.P.[C],
London, Ont.

THE DEVELOPMENT of ascites is a sign of serious liver decompensation. Control of ascites is a difficult problem in management. The life expectancy of a cirrhotic patient is short when repeated paracenteses are required for control of ascites. Repeated paracenteses cause marked protein depletion and occasionally may precipitate hepatic coma. It is generally agreed that paracentesis should be reserved for those cases in which medical management fails to control the ascites.

The relative importance of portal vein hypertension, decreased plasma osmotic pressure due to low plasma proteins, increased antidiuretic hormone activity and renal sodium retention in the development of ascites has not been established. Treatment of ascites due to cirrhosis has been variable owing to the numerous factors involved in its pathogenesis. Ascites has been decreased by medical management, consisting of abstinence of alcoholic intake and a high protein diet with vitamin supplements.[1] The effects of salt-free intravenous albumin infusions on ascites are transient. Decreasing the portal vein hypertension by surgical means is contraindicated in the presence of ascites. The development of potent agents producing renal sodium loss has been the most significant advance in the medical therapy of ascites.

Renal retention of sodium is necessary for the development of ascites in patients with hepatic cirrhosis. The decompensated cirrhotic patient retains sodium on a low sodium intake. Onen[2] has shown that the majority of decompensated cirrhotics have a markedly lowered glomerular filtration rate, which decreases the filtered load of sodium presented to the renal tubules. Increased production and increased urinary excretion of aldosterone have been demonstrated in the cirrhotic patient with ascites.[3] Farrell[4] reports that the secretion of aldosterone appears to be stimulated by a tropic factor which arises from the posterior commissure-pineal area of the brain stem. ACTH is of minor importance in the control of aldosterone secretion.[5] Recent reports[6, 7] suggest the kidney as a factor involved in control of aldosterone secretion. It appears likely that some function of intravascular volume provides the stimulus to increase aldosterone production.[8] Aldosterone increases renal sodium reabsorption, probably in the distal tubule. These two factors, the low glomerular filtration rate and the increased aldosterone production, are probably significant in producing the marked renal sodium retention in the cirrhotic patient with ascites.

Many drugs that stimulate renal sodium excretion, combined with a low sodium intake, have been used in the treatment of cirrhotic ascites. Mercurial diuretics have been effective in some cases, but the long-term results have not been impressive. The benzothiadiazine derivatives have been more effective, but they produce hypokalemia with extracellular alkalosis which is poorly tolerated by the cirrhotic patient. The increased urinary potassium loss in cirrhotics treated by the benzothiadiazines is frequently not prevented by increasing the oral intake of potassium.[9] Steroids of the 17-spirolactone group have been shown to inhibit the effects of aldosterone on the renal tubule, producing increased renal sodium excretion. Short-term studies have shown the effectiveness of the 17-spirolactones in the treatment of ascites due to cirrhosis.[10, 11] Orally effective spironolactone (Aldactone) is the most effective aldosterone-inhibiting drug at present available. This study concerns the long-term effect of spironolactone in the treatment of ascites due to cirrhosis. Spironolactone was used in three patients and combined with chlorthalidone (Hygroton) during the course of treatment in one patient. The long-term effect of spironolactone on sodium, potassium, water and acid-base balance was studied.

PLAN OF INVESTIGATION

Three cirrhotic patients with ascites were chosen for study. Prior to study on a metabolic ward the patients had demonstrated resistance to therapy directed toward decreasing the ascites. A constant sodium and potassium diet was used throughout the study. Frequent determinations of sodium and potassium were carried out on duplicate diets and the mean value of these determinations was recorded as the intake of sodium and potassium. The patients were on a constant diet at least five days before the studies. Twenty-four-hour urinary sodium, potassium and chloride determinations were performed throughout the study. Diet protein varied from 30 to 90 g. per day. The caloric intake was approximately 2000 calories daily. The oral fluid intake was recorded and was unrestricted.

Twenty-four-hour urinary creatinine clearances were determined weekly. Serum sodium, potassium, chlorides, CO_2 combining power, hematocrit, plasma proteins and blood urea values were determined weekly. Venous blood pH was estimated frequently throughout the study. Drug therapy varied, depending upon the response of each patient.

CASE HISTORIES AND RESULTS OF INVESTIGATION

CASE 1.—A 62-year-old white male was seen in 1957 with gouty arthritis and hypertensive cardiovascular disease (blood pressure was 186/100 mm. Hg). His liver and spleen were not palpable. In May

*From the Clinical Investigation Unit, Westminster Hospital, London, Ontario; Department of Veterans Affairs, Canada.

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1958, he developed weakness, anorexia and vomiting. Obstructive jaundice was present. He had marked ascites and the liver was palpable 3 cm. below the right costal margin. In July 1959, 4500 c.c. of peritoneal fluid was removed. Paracentesis was repeated in September 1959, and 6000 c.c. of fluid was obtained. A low sodium diet, 1 g. of chlorothiazide daily and intermittent administration of intravenous albumin (total dose 600 g.) from September 1959 to February 1960 did not control the ascites. The spleen was palpable in February 1960, when he was admitted to hospital with an upper gastrointestinal tract hemorrhage and hepatic coma. The blood ammonia value was 530 μg. % and the hematocrit 29%. Treatment with oral neomycin and intravenous glucose in water produced marked improvement, the blood ammonia level decreasing to 112 μg. %. The response to spironolactone therapy was studied from March 28 to June 16, 1960 (81 days). An episode of hepatic coma temporarily interrupted the study on the 37th day.

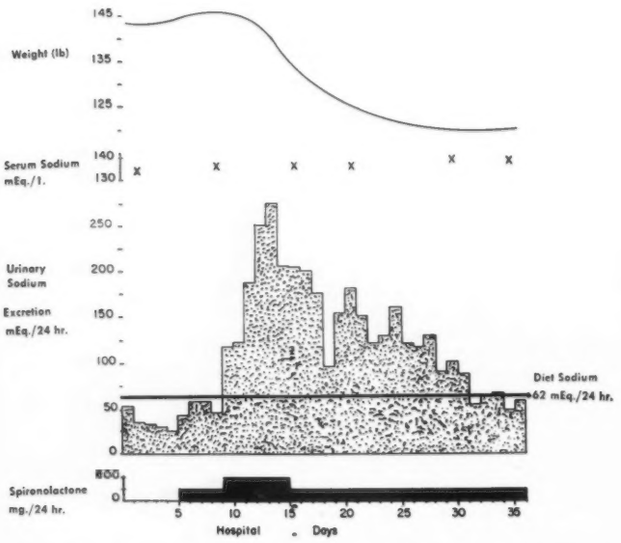

Fig. 1—Sodium balance in Case 1 prior to the episode of hepatic coma. The patient was a 62-year-old man with cirrhosis of the liver and ascites who was treated by spironolactone (Aldactone).

Fig. 1 illustrates this patient's sodium balance prior to the episode of hepatic coma. Before spironolactone therapy was begun, the patient was retaining sodium and gaining weight. Administration of spironolactone, 400 mg. per day for four days, produced a slight increase in urinary sodium excretion. The dose was increased to 800 mg. daily, and this produced a marked increase in urinary sodium excretion with concomitant fall in weight. Spironolactone was reduced to 400 mg. daily on the 15th day, and urinary sodium excretion remained greater than the dietary intake of sodium from the 15th to the 36th day. The serum sodium remained within normal limits.

Fig 2 shows the sodium balance after the episode of hepatic coma. Increased urinary excretion of sodium was maintained on a dose of 400 mg. of spironolactone a day. Reduction of the dose of spironolactone to 200 mg. daily produced a positive sodium balance. A dose of 300 mg. a day at the end of the study resulted in slight negative sodium balance. The serum sodium throughout the entire study remained within normal

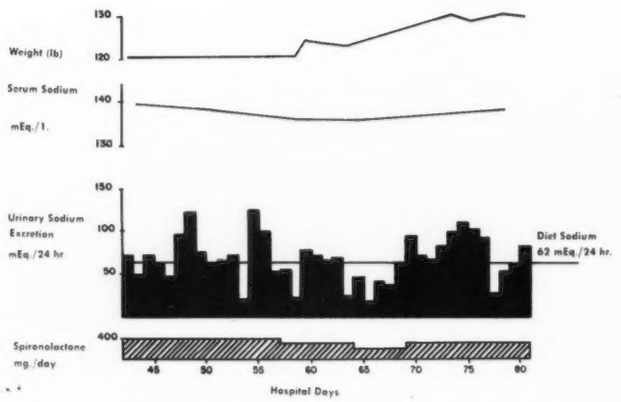

Fig. 2.—Sodium balance in Case 1 after the episode of hepatic coma.

limits. Spironolactone therapy completely controlled the ascites in this patient.

Fig. 3 shows the potassium and water balance prior to the episode of hepatic coma. The urinary potassium excretion was approximately the same as the dietary intake during spironolactone therapy. The serum potassium increased to 5.5 mEq./l. on one occasion but was otherwise within normal limits. There was a marked increase in urinary volume concomitant with the increased sodium excretion. Before therapy the mean fluid intake was 522 c.c. greater than the mean urinary output per 24-hour period. After spironolactone therapy the mean urinary output was 185 c.c. greater than the mean oral fluid intake per 24-hour period.

Fig. 4 shows the potassium balance after the episode of hepatic coma. Reduction of spironolactone therapy to 300 mg. per day produced an increased urinary potassium excretion. The serum potassium level remained within normal limits throughout the study. The CO_2 combining power decreased slightly at the termination of this study.

Fig. 5 shows the weekly hematocrit and plasma protein values in relation to the therapy and diet. There was a gradual increase in both plasma albumin and globulin. The hematocrit value increased slightly, but not to the degree that the plasma proteins increased. Hepatic coma occurred when the dietary protein reached 90 g. per day.

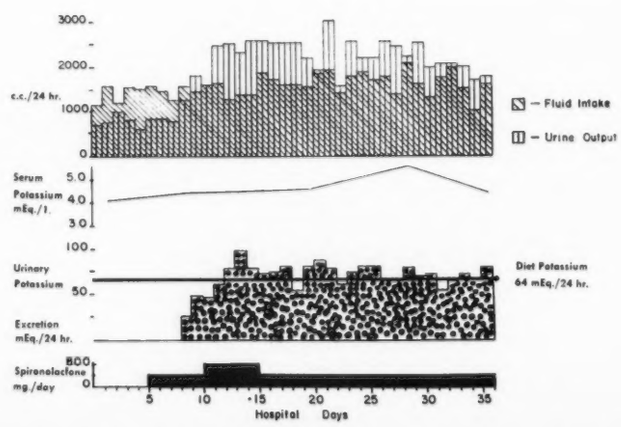

Fig. 3.—Potassium balance in Case 1 prior to the episode of hepatic coma.

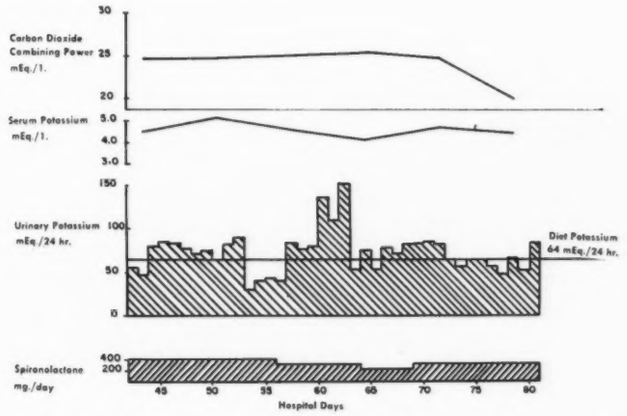

Fig. 4.—Potassium balance in Case 1 after the episode of hepatic coma.

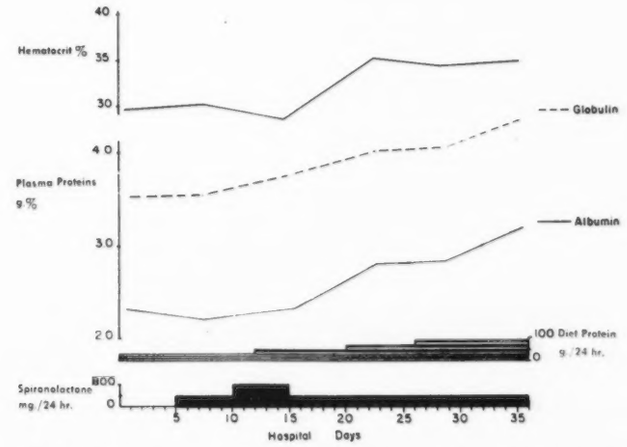

Fig. 5.—Hematocrit, plasma proteins and diet protein values in Case 1 prior to the episode of hepatic coma.

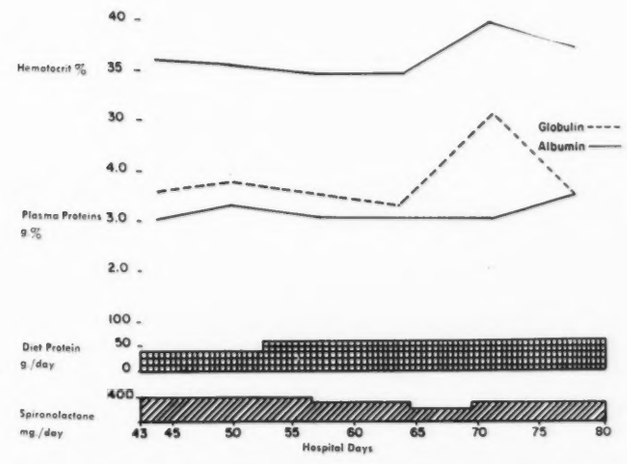

Fig. 6.—Hematocrit, plasma proteins and diet protein values in Case 1 after the episode of hepatic coma.

Fig. 6 records the weekly plasma proteins and hematocrit levels after the episode of hepatic coma. With the patient on a diet of 60 g. of protein per day, the plasma albumin continued to increase, and at the end of the study the plasma globulin and albumin values were equal. The hematocrit increased slightly.

The mean 24-hour fluid intake during the period after hepatic coma was 1788 c.c. The mean urinary output during the same period was 1735 c.c.

TABLE I.—LIVER FUNCTION TESTS IN CASE 1

Date	*Bilirubin (mg.%)*	*% BSP retention (after 45 min.)*	*Cephalin-cholesterol flocculation (after 48 hr.)*	*Thymol turbidity (units)*
Sept. 1959	1.9	23.4	3+	4.7
Feb. 1960	2.5	28.0	4+	13.0
May 1960	0.8	13.8	4+	13.8

Table I shows the results of representative liver function tests during the period of study. The serum bilirubin gradually decreased; bromsulphthalein retention decreased; and the 48-hour cephalin-cholesterol flocculation and thymol turbidity values increased in keeping with the elevated plasma globulin.

The glomerular filtration rate, as measured by the endogenous creatinine clearance, increased slightly during spironolactone therapy.

The patient was discharged on spironolactone 100 mg. three times daily. He was readmitted eight days later in hepatic coma, produced by a high protein intake. He responded well to treatment for hepatic coma. He was discharged on a regimen of chlorothiazide, 0.5 g. daily for four days followed by four days with no medication. He has continued to take chlorothiazide intermittently, and in February 1961 was free from edema and ascites. The liver and spleen remained palpable.

CASE 2.—A 66-year-old white man had an upper gastrointestinal hemorrhage in May 1958. He recovered on conservative management. After the upper gastrointestinal bleeding he had frequent episodes of epigastric pain, before meals and at night, which were relieved by food. In January 1960, he noted swelling of his abdomen and ankles. He was admitted to hospital in May 1960, because of increased ascites and edema.

Physical examination revealed marked edema of the legs, extending into the soft tissues of the abdomen, and massive ascites. The upper extremities were thin. Palmar erythema and gynecomastia were present. The liver was palpable 4 cm. below the costal margin. The spleen was not palpable.

An upper gastrointestinal series showed deformity of the duodenal cap with no evidence of esophageal varices.

The patient responded to intitial treatment of a low sodium diet and chlorothiazide 1 g. per day, gradually losing 18 lb. in weight. Before the metabolic balance study, ascites and peripheral edema remained a problem in management. The patient's response to therapy was studied from June 8, 1960, to September 5, 1960 (93 days).

Fig. 7 records the results of the complete sodium balance study in Case 2. Before therapy there was a slight tendency to retain sodium. Institution of benzydroflumethiazide (Naturetin) therapy produced a marked intitial increase in the 24-hour urinary sodium excretion to 205 mEq. Continued therapy with benzydroflumethiazide had little effect on urinary sodium excretion. Spironolactone therapy, after the benzydroflumethiazide was discontinued, produced a prolonged increased urinary sodium excretion. Termination of spironolactone therapy resulted in a marked decrease in urinary sodium excretion. Re-institution of 200 mg.

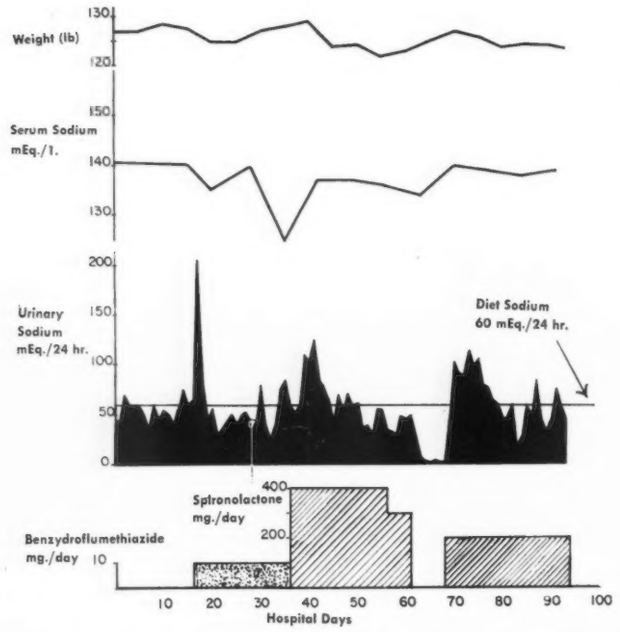

Fig. 7.—Sodium balance in Case 2. The patient was a 66-year-old man with cirrhosis of the liver and ascites.

of spironolactone per day produced an increased urinary sodium excretion. The serum sodium level decreased markedly when the patient was on benzydroflumethiazide therapy and returned to the normal range when he was on spironolactone. The patient's weight varied directly with the urinary sodium excretion. His abdomen was normal and there was no peripheral edema at the end of the 93-day study.

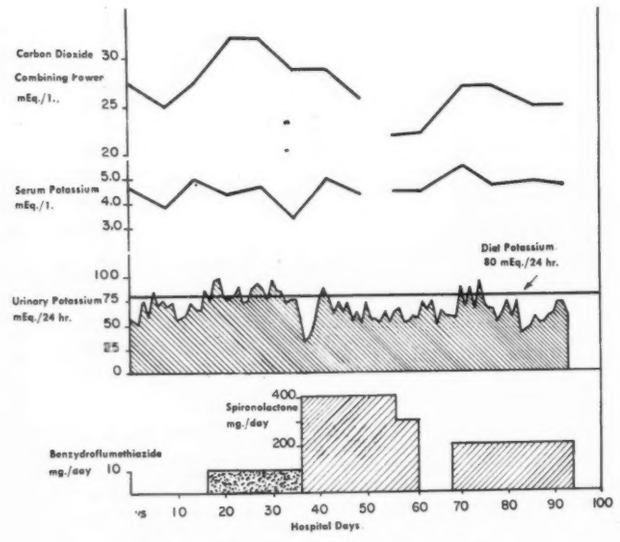

Fig. 8.—Potassium balance in Case 2.

Fig. 8 shows the potassium balance during the 93-day study period in Case 2. Before treatment the urinary excretion of potassium was slightly less than the oral intake. Benzydroflumethiazide therapy produced a urinary potassium loss in excess of the dietary intake of potassium. Termination of benzydroflumethiazide and the institution of spironolactone therapy produced a marked decrease in the urinary potassium excretion. While the patient was on long-term spironolactone therapy, the urinary potassium excretion was slightly less than the oral intake. Serum potassium decreased on benzydroflumethiazide therapy but remained normal throughout the remainder of the study during spironolactone therapy. The CO_2 combining power reflected the urinary potassium loss—increasing with benzydroflumethiazide therapy and returning to normal levels during the spironolactone therapy.

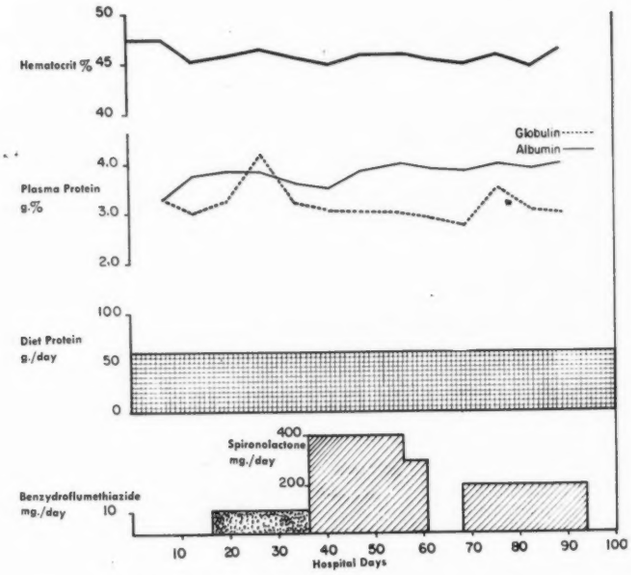

Fig. 9—Hematocrit, plasma proteins and diet protein values in Case 2.

Fig. 9 gives the hematocrit values and plasma protein levels in relation to dietary intake of protein and to therapy. During the period of study there was a gradual increase in the plasma albumin and a gradual decrease in the plasma globulin values. The hematocrit remained relatively unchanged.

TABLE II.—LIVER FUNCTION TESTS IN CASE 2

Date	*Bilirubin (mg.%)*	*% BSP retention (after 45 min.)*	*Cephalin-cholesteral flocculation (after 48 hr.)*	*Thymol turbidity (units)*
May 1960	2.0	24.0	3+	13.8
Aug. 1960	1.0	14.0	3+	8.7
Sept. 1960	0.8	15.4	1+	7.3

Table II reveals the results of representative liver function tests during the period of study. There was improvement, as judged by the four liver function tests performed, as the ascites and edema were controlled by therapy.

The values for venous blood pH and glomerular filtration rate (endogenous creatinine clearance) showed a tendency to decrease during spironolactone therapy.

The patient was discharged from hospital free from ascites and edema in September 1960, on spironolactone, 100 mg. twice daily. He was re-admitted with an upper gastrointestinal hemorrhage in October 1960. At that time his hematocrit value was 32%. Spironolactone was discontinued, and there was a rapid accumulation of ascitic fluid. Bleeding stopped, and he recovered without transfusion. Spironolactone therapy completely cleared the ascites, and he was discharged on 400 mg. per day.

The patient was re-admitted to hospital on January 4, 1961, with a recurrence of epigastric pain. There was no ascites. He responded well to ulcer management. Spironolactone was again discontinued, to determine the necessity of this treatment. He developed ascites again and once more responded to spironolactone, the ascites disappearing completely. Epigastric pain did not recur when spironolactone therapy was re-instituted during peptic ulcer management. The spleen became palpable in February 1961.

CASE 3.—A 58-year-old white man was known to have hypertensive cardiovascular disease since 1953. During 1955, he suffered a posterior myocardial infarction complicated by an episode of complete heart block. He remained well until February 1960, when he developed dyspnea and swelling of the abdomen and feet. A low sodium diet, digitalization and intermittent use of mercurial diuretics were initially effective in controlling the fluid retention. Gradually he became refractory to mercurial diuretics and was admitted to hospital in October 1960, with massive peripheral edema and ascites. His blood pressure was 190/120 mm. Hg. He remained unresponsive to mercurial diuretics in hospital. Chlorthalidone (Hygroton) produced an increased urinary output and a loss of 10 lb. in weight. He then became refractory to chlorthalidone therapy. The patient was treated on the metabolic ward from November 11, 1960, to February 2, 1961 (84 days).

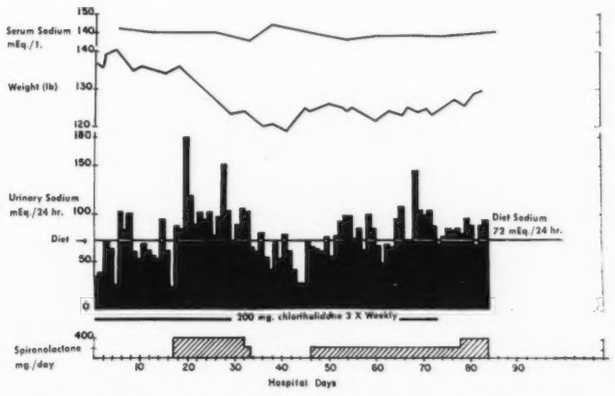

Fig. 10.—Sodium balance in Case 3. This patient was a 58-year-old man with hypertension and hepatic cirrhosis.

Fig. 10 records the results of the sodium balance study in Case 3. Chlorthalidone, 200 mg. three times weekly, produced a very slight increase in renal sodium excretion. The addition of spironolactone therapy produced a marked increase in sodium excretion. When spironolactone therapy was discontinued and the patient was maintained on chlorthalidone, sodium retention occurred. Spironolactone therapy was reinstituted on the 47th day, and increased sodium excretion again resulted. Chlorthalidone was discontinued on the 73rd day, and renal sodium excretion was maintained by use of spironolactone. The serum sodium level remained within normal limits throughout the study. His weight varied directly with the amount of renal sodium excretion.

Fig. 11 shows the potassium balance in Case 3. Renal potassium excretion exceeded the dietary intake, when chlorthalidone was the sole treatment. Spironolactone therapy in addition to chlorthalidone decreased the renal potassium excretion to levels which were much lower than the dietary intake. Hyperkalemia (6.2 mEq./l.) occurred and spironolactone was discontinued. This resulted in a marked increase in renal potassium excretion during the mid part of the study, while the patient was on chlorthalidone. Spironolactone was re-instituted on the 47th day, and decreased renal potassium excretion resulted. After chlorthalidone was discontinued on the 73rd day, there was a further reduction of renal potassium excretion.

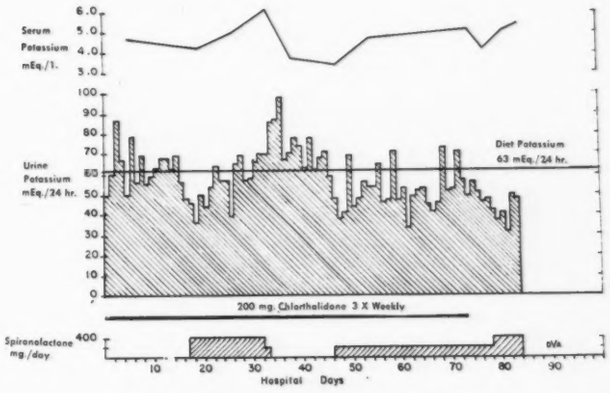

Fig. 11.—Potassium balance in Case 3.

Serum potassium decreased when chlorthalidone was used alone at the beginning of the study. The addition of spironolactone markedly increased the serum potassium, which decreased promptly when the spironolactone was discontinued. Serum potassium gradually increased when spironolactone therapy was re-instituted on the 47th day. The serum potassium increased still further when chlorthalidone was discontinued near the end of the study.

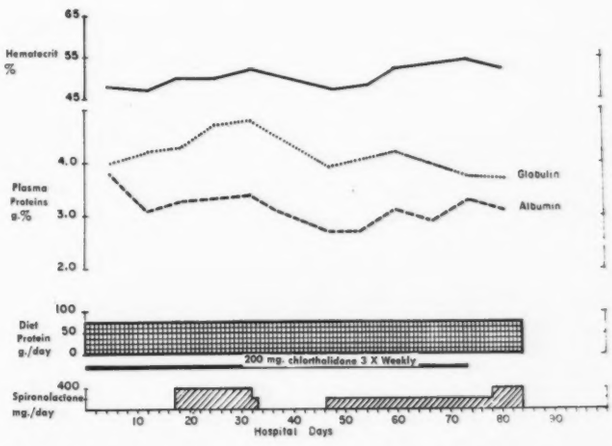

Fig. 12.—Hematocrit, plasma proteins and diet protein values in Case 3.

Fig. 12 shows the hematocrit and plasma protein values in relation to therapy in Case 3. There was a slight increase in the hematocrit during the study period. The plasma proteins remained relatively unchanged.

Fig. 13 gives the values for glomerular filtration rate (endogenous creatinine clearance), CO_2 combining power and blood pH, in relation to therapy. When the patient was on chlorthalidone therapy, the CO_2 combining power rose slightly and decreased when spirono-

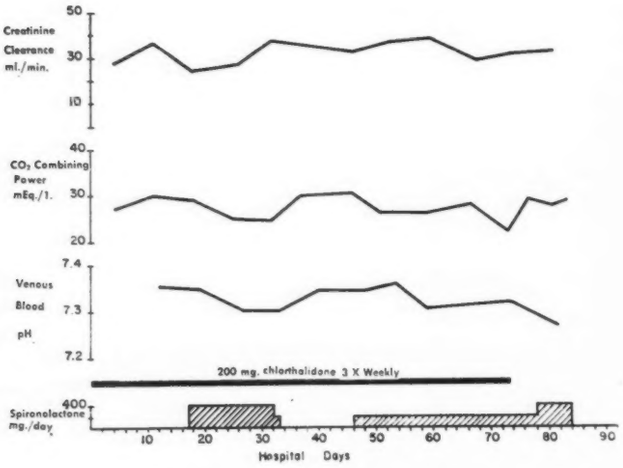

Fig. 13.—Endogenous creatinine clearance, CO_2 combining power and venous blood pH values in Case 3.

lactone therapy was added. Venous blood pH varied directly with the changes in the CO_2 combining power. The glomerular filtration rate remained low and generally unchanged throughout the study.

TABLE III.—LIVER FUNCTION TESTS IN CASE 3

Date	*Bilirubin (mg.%)*	*% BSP retention (after 45 min.)*	*Cephalin-cholesterol flocculation (after 48 hr.)*	*Thymol turbidity (units)*
Oct. 1960	2.5	—	3+	7.1
Dec. 1960	1.0	11.7	3+	14.7
Feb. 1961	0.7	10.5	4+	9.2

Table III presents the liver function tests during the period of study in Case 3. The serum bilirubin decreased, but the other liver function tests performed were little changed.

There was no clinical evidence of ascites after the initial course of spironolactone therapy in this patient. His liver and spleen became easily palpable as his ascites decreased. A liver biopsy on the 56th day of therapy revealed cirrhosis of the liver. The patient remained free from ascites during the remainder of the study. Slight edema of the feet persisted. He was discharged on February 3, 1961, on chlorothiazide 1 g. per day and spironolactone 200 mg. daily. He was re-admitted on February 7, 1961, with a complete flaccid right hemiplegia. He died 10 days later.

Postmortem examination revealed a large left cerebral infarct secondary to occlusion of the left internal carotid artery. There was a large posterior myocardial infarct and old mural thrombi in both ventricles. Laennec's cirrhosis of the liver was present. Recent thrombosis of the abdominal aorta was noted with complete obstruction at the bifurcation and left renal artery.

DISCUSSION

Spironolactone was shown to be effective in the long-term treatment (up to eight months) of ascites due to cirrhosis. Renal sodium excretion increased on the 3rd to 4th day of treatment. This response continued until the abdomen was completely free of fluid on clinical examination. The maintenance dose varied from 200 to 400 mg. daily. Spironolactone was effective in producing increased urinary sodium excretion, after a benzothiadiazine derivative and a phthalimidine derivative had previously failed. Hyponatremia did not occur. Hyponatremia has been reported with spironolactone therapy, and has been effectively treated by limiting the oral fluid intake to 1000 c.c. daily.[12] Hyponatremia is more likely to occur when a benzothiadiazine is combined with a 17-spirolactone during therapy.[10] Shaldon, McLaren and Sherlock[10] have effectively controlled the hyponatremia associated with spironolactone administration by increasing the renal osmotic load with intravenous mannitol, producing an increased renal free water clearance.

Marked renal sodium retention occurred when spironolactone was discontinued in Case 2. This suggested an increased aldosterone production when spironolactone was used to block the effect of aldosterone on the renal tubule. Walfish *et al.*[13] have reported increased urinary aldosterone excretion in cirrhotic patients with ascites treated by spironolactone. The initial abnormal liver function tests and marked response to spironolactone in Case 3 suggested that cirrhosis was the major factor in sodium retention in this case. The response to aldosterone-inhibiting drugs is greater in cirrhotic patients with edema than in patients in whom the sodium retention is secondary to congestive heart failure.[14]

Spironolactone did not produce renal potassium retention in the two patients with good renal function during long-term therapy. Renal function was poor in Case 3, and in this patient spironolactone caused potassium retention with hyperkalemia which was quickly reversed by discontinuing the drug. Potassium was retained despite the simultaneous administration of chlorthalidone, which had previously been shown to increase urinary potassium excretion. Changes in the glomerular filtration rate, estimated by endogenous creatinine clearances, were variable in the three cases. The slight decrease in the CO_2 combining power and decreased venous blood pH values during long-term spironolactone therapy suggests that the drug might inhibit renal hydrogen ion excretion. Hydrogen ion and potassium compete for excretion when sodium is reabsorbed under the influence of aldosterone in the distal renal tubule. An aldosterone-inhibiting drug would, therefore, be expected to decrease hydrogen ion excretion.

The increase in plasma albumin and the improvement in the liver function test results during therapy is in keeping with previously reported cases in which medical management decreased the ascites in patients with cirrhosis associated with alcoholism.[15] The slight changes in the hematocrit suggest that the increase in the plasma proteins was real, rather than due to the hemoconcentration that might be produced by therapy.

High protein diets frequently precipitate neuropsychiatric changes in a cirrhotic patient and

should be used cautiously. Cirrhotic patients will retain protein on a diet of less than 80 g. protein per day.[16] Cases 1 and 2 demonstrated a marked improvement in the plasma protein levels as ascites decreased while the protein intake was approximately 60 g. per day.

Tyor and Sieker[17] report that anoxemia, hyperventilation and respiratory extracellular alkalosis contribute significantly to the disordered consciousness frequently seen in cirrhotic patients. Metabolic extracellular alkalosis may also precipitate hepatic coma.[18] Frequently the metabolic extracellular alkalosis, produced by potassium loss due to benzothiadiazine therapy, cannot be prevented by potassium supplements.[9] Spironolactone is effective in preventing extracellular alkalosis in cirrhotic patients treated with benzothiadiazines and it seems advisable to prevent this complication of diuretic therapy.

It is Pitts'[19] hypothesis that there is a single mechanism for renal sodium reabsorption supplied by multiple sources of energy and that the different diuretic drugs block different sources of energy, thus explaining the varied activity of the diuretic drugs and the potentiating effect of two or more drugs on sodium excretion. Mercury probably blocks sodium reabsorption in the proximal tubule because of the increased free water clearance and the acid urine produced. The carbonic-anhydrase-inhibiting drugs block hydrogen ion excretion and therefore decrease sodium reabsorption and produce a higher urine pH than do mercurials. The benzothiadiazines are weak carbonic anhydrase inhibitors and have an action similar to that of the mercurials on the proximal tubule, as shown by free water clearance studies.[19] The 17-spironolactones by inhibiting aldosterone activity in the distal renal tubule block still another mechanism for sodium reabsorption and can potentiate renal sodium loss when given simultaneously with other diuretic agents. The varied and increased effect of the presently available diuretic drugs on renal function stresses the need for close observation of electrolyte and acid-base balance when diuretic agents are used alone or in combination.

It has become apparent that the choice of a diuretic agent in edematous and ascitic states depends on the underlying disease process and the pathological physiology producing the abnormal renal retention of sodium and water. In the decompensated cirrhotic there is good evidence[3] of a marked increase in aldosterone production, suggesting that the aldosterone-inhibiting drugs should be effective in treating the ascites of these patients. Indeed, short-term studies have shown this to be so.[10, 11] The results of a long-term study of treatment with an aldosterone antagonist, which have been described in this report, suggest that there is a definite place for the 17-spironolactone group of drugs in the treatment of ascites due to cirrhosis.

SUMMARY

Spironolactone (Aldactone) therapy was shown to be effective in the long-term treatment of ascites due to cirrhosis of the liver. Complications due to spironolactone therapy were minimal; hyperkalemia was observed in one case with poor renal function. The diuretic therapy of ascites due to cirrhosis has been discussed.

The author wishes to express appreciation to Dr. J. A. Lewis, Chief of Medical Service, Westminster Hospital, and Dr. D. M. Nicholls of the Clinical Investigation Unit, Westminster Hospital, for their criticism and advice during the preparation of this paper.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

CANCER OF THE STOMACH

Billroth did the first successful gastric resection twenty-nine years ago.

In 1839 Cruheilhier first described ulcer, distinguishing it from cancer, and suggested the possibility of the development of cancer upon the base of an ulcer. In 1840 Rokitansky also expressed the opinion that the one condition might be implanted upon the other.

In 1848 Dittrich reported six cases of cancer developing in the immediate vicinity of an active or healed ulcer, two of association of cancer and ulcer, and two of circumscribed cancer in the margin of an ulcer.

In 1878 Lebert stated that cancerous transformation occurred in 9 per cent. of ulcers, while Zenker, in 1882, believed that all cases of gastric cancer were secondary to ulceration.—Herbert A. Bruce, *Canad. M. A. J.*, 1: 805, 1911.

INTERPRETATION OF THE SIGNIFICANCE OF A POSITIVE SENSITIZED SHEEP CELL AGGLUTINATION TEST IN THE DIFFERENTIAL DIAGNOSIS OF RHEUMATIC DISORDERS*

NORMAN A. HINTON, M.D., C.M., M.Sc., Dip. Bact. and H. GARFIELD KELLY, M.D., C.M., F.R.C.P.[C], F.A.C.P., *Kingston, Ont.*

HIGH molecular weight gamma globulins with a sedimentation constant of about 19S form an immunologically heterogeneous group of plasma proteins.[6] Within this group are found clearly defined antibodies of varying specificity, including cold agglutinins, Wassermann antibody, antityphoid antibody, the heterophil antibody found in infectious mononucleosis and isohemagglutinins.[4] Also within this group are to be found 19S globulins whose production has come to be recognized as a feature of established rheumatoid arthritis. These globulins may be identified, not only by their size, but by an antibody-like capacity to combine with low molecular weight gamma globulin, human or animal.[9]

Early enthusiasm regarding the diagnostic and pathogenetic significance of these components was associated with the evolution of the term "rheumatoid factor", a term which carries with it implications of a specific relationship between this factor and rheumatoid arthritis. Unfortunately, it has now become apparent that the production of this class of reactive macroglobulins is not a feature restricted to rheumatoid arthritis but is observed in a number of disease states, positive tests being recorded with considerable frequency in various collagen diseases, sarcoidosis, syphilis, hepatic disease and various virus infections.[2, 3, 11, 13]

Although no remarkable differences in physical characteristics between "rheumatoid factors" isolated from rheumatoid and non-rheumatoid patients have been observed[1, 11] (with the possible exception of the ease of precipitation in the cold of the factor seen in lupus erythematosus[14]), when careful serologic studies are carried out, it is apparent that in terms of the capacity to combine with gamma globulin under various conditions, the term "rheumatoid factor" embraces a heterogeneous collection of macroglobulins.

Lospalluto and Ziff[12] have reported the isolation of two distinct "rheumatoid factors" by ion exchange chromatography, one of which agglutinated both sheep cells sensitized by rabbit globulin and latex particles sensitized by human globulin and the other reacting only in the latex fixation test. Heimer, Schwartz and Freyberg[8] have demonstrated five distinct macroglobulins with the characteristics of "rheumatoid factor" in the serum of one patient with rheumatoid arthritis.[8] Fudenberg and Kunkel,[5] using a test system in which the sensitizing agent was anti-Rh antibody derived from a series of individuals, observed no fewer than seven types of "rheumatoid factors" in a group of 24 test sera.[5]

Thus it is clear that the various tests used for the purpose of detecting the "rheumatoid factor" will give positive reactions with a variety of closely related macroglobulins in a variety of disease states. This is not to deny the possibility that a particular macroglobulin or group of macroglobulins may be specifically associated with rheumatoid arthritis. However, the fact is that the tests we have at our disposal apparently are not selective enough at the present time to detect such a factor if it exists.

Under these conditions it would seem important to redefine the term "false positive reaction", and reserve it to cover positive tests which are not due to the presence of a reactive macroglobulin. There is no doubt that in the delicately balanced systems in use, a positive test, usually in low titre, may result from differences in stabilizing factors, protein-protein reactions, the presence of complement and conglutinin. Definition of the incidence of such false-positive tests will be a major factor in setting, probably in an arbitrary fashion, the initial dilution of serum in which a positive test would be considered significant. Such a positive reaction may then be interpreted simply as indicating the presence of a macroglobulin which has the capacity to combine with low molecular weight gamma globulin.

Although the production of such a reactive macroglobulin is clearly not specific for rheumatoid arthritis, the tendency to deny the diagnostic usefulness of this test altogether seems to us a short-sighted attitude. The results of only a very limited number of all tests performed in the clinical laboratory may be interpreted as unequivocal proof of the presence of a specific disease state. The vast majority constitute evidence of varying importance which must be considered against the background of the natural history of the disease in that patient and an assessment of various parameters of the test as opposed to a simple positive or negative result.

This paper summarizes some of our experience with the continued use of the sensitized sheep cell agglutination test (SSCA test) and an attempt is made to evaluate the diagnostic significance of positive tests, taking into consideration the clinical condition of the patient, the amount of "rheumatoid factor" (as expressed by the height of the titre) and its fluctuation with time.

MATERIALS AND METHODS

The subjects included in this study were a group of 1012 individuals drawn from an arthritis outpatient clinic, from private practice and from patients admitted to the Kingston General Hospital.

*From the Departments of Bacteriology and Medicine, Queen's University, Kingston, Ont. This study was supported by the Canadian Arthritis and Rheumatism Society.

No attempt has been made to survey a cross-section of the general population. This is a selected group in the sense that all of the patients were sufficiently ill to seek medical attention and all suffered from some rheumatic disorder.

The technique of the sensitized sheep cell test used has been previously described.[10] It involves the separation of the euglobulin fraction of the test serum (precipitation by dilution with 0.0027 normal HCl), inactivation of this fraction at 56° C. for one half-hour and adsorption with sheep cell suspension. Serial dilutions of the reconstituted fraction are then mixed with a standard suspension of sensitized sheep red cells in buffered saline at pH 7, incubated at 37° C. for one hour and then at 5° C. overnight. The end point of the reaction is read by observing the pattern of settling of the cells in round bottomed cups in a perspex plate.

RESULTS

The distribution of positive SSCA tests in the study group is represented in Fig. 1. The patients

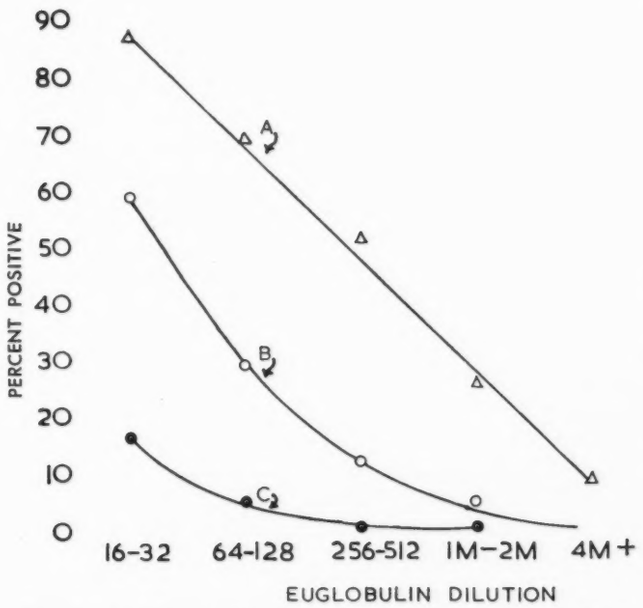

Fig. 1.—The distribution of SSCA titres in rheumatoid and non-rheumatoid subjects.

A—217 cases of definite rheumatoid arthritis. B—59 cases of possible and probable rheumatoid arthritis. C—736 other rheumatic disorders.

have been divided into three groups, 217 cases of definite rheumatoid arthritis, 59 cases of possible and probable rheumatoid arthritis and 736 cases of other rheumatic disorders. Patients with definite rheumatoid arthritis stand out as having not only the highest incidence of positive tests, but also a distribution of significantly higher titres than any other group. They are followed in this respect by the cases of probable and possible rheumatoid arthritis.

These data are supported by the work of many authors, and in the evaluation of the diagnostic significance of the SSCA test it must be recalled that without doubt a positive test, especially in high titre, is most frequently associated with rheumatoid arthritis.

High-titre positive tests are not, however, an exclusive feature of rheumatoid arthritis and, further, many cases of definite rheumatoid arthritis may show positive reactions only in low dilutions. To determine whether the behaviour of the titre with time might be of some help in evaluation, the initial titres obtained in 95 positive rheumatoid patients, and the titres six months later in these cases, have been contrasted in Fig. 2 with the

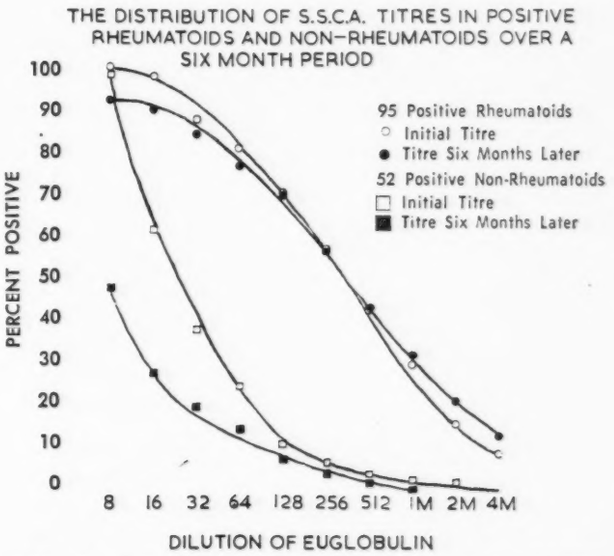

Fig. 2.—The distribution of SSCA titres in positive rheumatoid and non-rheumatoid subjects over a six-month period.

titres of 52 non-rheumatoid persons who were found to give a positive test, and their titres after six months. The level and stability of the titres in the cases of established rheumatoid arthritis is clearly demonstrated and contrasts sharply with the non-rheumatoid group in which the positive tests are not only clustered largely at a lower titre level, but also in nearly 50% of cases have become negative within six months. A closer examination of the patients in the non-rheumatoid group reveals that if all of the cases of diffuse collagen disease and ankylosing spondylitis are excluded, the remaining patients, with the exception of three, either became negative or showed a significant fall in titre at the second examination.

One patient with a titre of 1000 had generalized joint aches and pains but a specific diagnosis of viral hepatitis. His titre declined to a level of 8 within six weeks. A further six of the patients in this non-rheumatoid group were subsequently demonstrated to be suffering from serologically proven virus infection, mostly with adenoviruses. Three of these had titres of 1/8, two of 1/16, and one patient with Coxsackie virus myocarditis had a titre of 1/32. All of these patients became negative within a six-week period. Virus infection undoubtedly represents a source of a significant

number of low-titre positive reactions in the serologic tests designed for the study of rheumatoid arthritis and, unfortunately, without extensive investigation it would be very difficult to determine the exact number of patients in the non-rheumatoid group with virus infections, as many of them had minor febrile episodes, elevation of their sedimentation rates and some general complaints which could have been on this basis. Dresner and Trombly[3] have reported that of 35 patients with a variety of viral infections about 17% gave positive serum agglutination tests. With the very sensitive euglobulin-inhibition test the incidence of positive reactions declined to a low level in a 12-week period. Although the results were not expressed in terms of the titre, one can only suppose that, in fact, the decline in titre may have been more striking. These workers also showed that another important group with respect to the production of "rheumatoid factor" is made up of cases of hepatocellular disease. Their series of 96 cases showed 71% positive euglobulin-inhibition tests at some time, although only a quarter had a positive reaction in the serum agglutination tests. They were able to show that a positive test could be correlated with the activity of the liver disease, and that in 19 positive patients examined serially over a period of two to 10 months, 53% reverted to negative.

One can only agree with these workers that a number of non-rheumatoid disorders, especially virus infections and liver disease, are marked by the production of "rheumatoid factor", and it is clear that these positive tests are false-positive only in the sense that the test is being used in the study of rheumatoid arthritis. The more sensitive the test used, the more frequently will the non-rheumatoid-positive case be revealed. One must also agree, and this is supported by our data, that the positive test in the non-rheumatoid patient appears to occur only so long as the pathologic processes concerned are active. It is here, clearly, that a distinction arises between positive tests in patients with rheumatoid arthritis and positives in non-rheumatoid patients. Just as it is characteristic of the titre to decline in virus infection, so it appears characteristic for the test in progressive rheumatoid arthritis, a disease marked by a long-term evolution of the pathologic process, to be maintained for very significant periods of time. Just as joint pain and swelling are findings which take on added significance in the diagnosis of rheumatoid arthritis if these features persist for more than six weeks, so we would feel that the value of a positive SSCA test as one of the diagnostic criteria in rheumatoid arthritis would be considerably enhanced if a time factor were added to the assessment.

The positive SSCA tests which we have attempted to evaluate are recorded in Table I. Here the 1012 rheumatic patients are divided into groups on the basis of the clinical diagnosis and the results of a SSCA test. The diagnosis of rheumatoid arthritis was based on the criteria of the American Rheumatism Association, the results of the sheep cell test being excluded from consideration. Two of the clinical groups deserve some explanation. The first is composed of 195 cases classified as joint aches in various non-rheumatic disorders. These are patients who have been hospitalized for a wide variety of non-rheumatic disease states, in whom joint aches and pains have appeared during the course of their illness or have formed part of their total picture. In many of these cases the joint disturbance was a relatively minor incidental finding. The other group comprises 134 patients classified as having joint aches and pains. These are people whose primary complaint is a rheumatic one. None of these patients demonstrated any remarkable physical findings in their joints with the exception of aching and pain, and in none of these could a specific diagnosis be made. A large proportion of this group would be classified by many clinicians as psychosomatic rheumatism and

TABLE I.

DISTRIBUTION OF 1012 RHEUMATIC PATIENTS INTO GROUPS ON THE BASIS OF THE SSCA TEST AND THE CLINICAL DIAGNOSIS

Group	*No. of patients with indicated SSCA titre*					*Total Pos.*	*Total Neg.*	*Total Cases*
	4000+	*2M-1M*	*512-256*	*128-64*	*32-8*			
Rheumatoid arthritis								
Definite rheumatoid arthritis	20	38	53	39	38	188	28	217
Possible and probable rheumatoid arthritis	0	3	4	10	18	35	24	59
Miscellaneous arthritides (specific diagnosis established)								
Ankylosing spondylitis	0	0	0	3	5	8	24	32
Other collagen diseases	0	2	0	4	10	16	30	46
Degenerative joint disease	0	0	0	4	21	25	191	216
Miscellaneous specific rheumatic diseases	0	*0	1	3	12	16	97	113
Joint aches in various non-rheumatic disorders	0	2	1	8	18	29	166	195
Joint aches and pains (specific diagnosis not established)	0	0	0	7	16	23	111	134
Total cases	20	45	59	78	138	340	672	1012

undoubtedly in a number of the cases a factor of nervous tension is involved.

A total of 340 positive reactions were recorded. Twenty patients, when initially seen, had a titre of over 4000 in the SSCA test. It is interesting to note that all of these patients were clinically diagnosed as definite rheumatoid arthritis. This is not to deny that other workers have recorded very high titres in diseases other than rheumatoid arthritis, but it is perfectly clear that a very high SSCA titre counts strongly in the diagnosis of rheumatoid arthritis.

Forty-five patients had titres between 2000 and 1000, and of these 41 were clinically diagnosed as rheumatoid arthritis. Two of the remaining patients were suffering from diffuse collagen disease; one had disseminated lupus erythematosus and the other had periarteritis nodosa. The joint involvement was minimal in both of these patients, and the differentiation of the disease state from rheumatoid arthritis was not difficult. Of the two final positive cases, one was a patient with an acute viral hepatitis in which the titre was seen to decline fairly rapidly from 1/1000 to a level of less than 16, and the other had a viral infection of the upper respiratory tract in which, although a specific diagnosis was not made, bacterial infection was excluded by culture and the course of the disease was compatible with a virus infection. The titre was seen to have declined within two weeks to a level of 32.

A total of 59 patients were seen with initial titres between 512 and 256, and of these 57 were clinically diagnosed as rheumatoid arthritis. One of the remaining positive tests was observed in a patient with progressive cirrhosis in whom the titre was again seen to decline as the active liver damage appeared to subside. The other positive test was in a patient with clearly defined gout.

Thus, of 124 patients with titres higher than 256, 111 fell into the clinical category of definite rheumatoid arthritis. Seven fulfilled the criteria of probable or possible rheumatoid arthritis, and in these the high sheep cell titre would tend to support the diagnosis. Specific diagnoses were possible in the remaining six cases, and the diagnosis of rheumatoid arthritis could be excluded.

Seventy-eight patients were seen to have titres between 128 and 64. Thirty-nine of these were classified on clinical grounds as cases of definite rheumatoid arthritis, and in a further 10 cases the clinical diagnosis of possible or probable rheumatoid arthritis was strengthened by the finding of a positive sensitized sheep cell test. Three more patients with positive tests in this group were diagnosed as cases of ankylosing spondylitis. In four more, a diagnosis of "collagen disease" was made, three of these being cases of acute rheumatic fever. The incidence of positive tests is clearly established in the group represented by the latter seven cases, and the diagnosis presented no problem in differentiation from rheumatoid arthritis. Seven further patients presented no diagnostic problems; these included one case of gout, two cases of frozen shoulder and four of degenerative joint disease.

The remaining 15 patients represent somewhat more of a problem. The positive test is explicable in one of these on the basis of active liver disease, but in the remainder the presence of liver disease or virus infection was not definitively established. With the eight patients suffering from a variety of non-rheumatic disorders the probability is high that some disease state other than rheumatoid arthritis is associated with the production of a reactive macroglobulin giving rise to a positive test, and in all instances the joint findings can be explained on the basis of the specific diagnosis that has been made, although one would be concerned if the evolution of the joint symptoms did not follow the course of the primary disease. The remaining seven patients fall into the category of patients in whom the possibility of evolving rheumatoid arthritis cannot be excluded and in whom a positive test would tend to increase the diagnostic suspicion.

Finally, we are presented with a large group of 138 patients with positive tests at a level of 1/32 or less. Fifty-six of these were clinically classified as rheumatoid arthritis. The remaining positive cases were made up in part of five cases of ankylosing spondylitis, 10 of collagen disease, mainly acute rheumatic fever, six of shoulder-hand syndrome, four of supraspinatus tendinitis, one case of gout, one case of acute infective arthritis and 21 cases of degenerative joint disease. A further 12 patients with positive tests represent a group suffering from clinical conditions primarily not rheumatic in nature and in whom the rheumatic complaints would be accepted as part of the total clinical picture. Thus, in the latter 62 cases, specific diagnoses can be made on clinical grounds and supported by a variety of laboratory data. Long-standing clinical practice would exclude these cases from a diagnosis of rheumatoid arthritis as a primary cause of that patient's particular illness. The remaining 16 cases with low-titre positive reactions, again, then represent non-specific clinical states in which one cannot exclude the possibility of evolving early rheumatoid arthritis.

This large group of 138 low-titre positives is, of course, the one in which non-specific positive reactions are most likely to be observed, i.e. positive reactions due to factors other than the presence of a reactive macroglobulin. The absence of a simple method which would allow the separation of such non-specific positives from true positive reactions imposes the necessity of making interpretations with this source of error in mind. This problem has been approached in a number of laboratories by requiring a higher initial dilution of the serum than has been our practice. Values of 1/20 and 1/40 are not unusual starting dilutions. We have felt that useful information may be lost

by excluding low-titre reactions, and our experience has been that repeated tests over a period of time frequently allow a useful interpretation to be made.

DISCUSSION

Thus, it appears that if one discards from consideration the concept that a positive SSCA test is specific for rheumatoid arthritis and the test is simply considered as one of the criteria which must be weighed in making a diagnosis in this disease, it is seen that a consideration of the total clinical picture, the titre of the reaction and its behaviour with time, allows the diagnostic significance of a positive test to be set at different levels of priority dependent upon these other features, and the interpretation is thus not quite as confused as one might gather from a survey of the literature. We would be inclined to grant relatively high priority, in terms of the diagnosis of rheumatoid arthritis, to high-titre positive reactions, to positive tests at any level which are maintained for weeks or months, especially in those instances where the titre is rising, and to positive tests in patients who fulfill the diagnostic criteria for possible, probable or definite rheumatoid arthritis. A low priority would be granted positive tests observed in patients in whom a specific diagnosis can be made which will satisfactorily cover the signs and symptoms observed in that particular patient. The test would also assume greater significance in those patients in whom a specific diagnosis cannot be made.

The application of this scale of priorities to our series shows that of the 340 positive tests recorded, 188 of the patients tested fall into the clinical category of definite rheumatoid arthritis, and in a further 35 cases a diagnosis of possible or probable rheumatoid arthritis was made and in these instances, then, the positive sheep cell test would tend to weigh in favour of such a diagnosis.

A further 94 cases were encountered in which a specific clinical diagnosis could be made, and thus, in practical terms, a diagnosis of rheumatoid arthritis excluded. It is from this group that the 52 cases recorded in Fig. 2 were drawn and, by and large, the titres in these individuals were seen to decline with time, another factor which would tend to mitigate against the diagnosis of rheumatoid arthritis.

A rather striking illustration of the behaviour of the SSCA titre with time in this group was given by one patient who presented with a nine-year history of intermittent polyarthralgia and a four-month history of persistent pain in both knees, ankles and feet. Joint swelling and effusion was observed in both knees, together with slight swelling of the right ankle, a sedimentation rate of 35 mm. per hour, a serum uric acid of 10.1 mg. %, and a SSCA titre of 1/256. The acute inflammatory reaction characteristic of gout was not observed, nor was any evidence of such a reaction in the past obtained in a careful history.

A working diagnosis of rheumatoid arthritis was made, albeit with some reservations considering the high uric acid determination, and the patient was managed on salicylates, phenylbutazone and intra-articular steroid injections. Over the next five months, despite the observed continuing activity of the disease so that repeated intra-articular steroid was required, the SSCA titre was recorded at monthly intervals, 1/256, 1/32, 1/32, 1/16, negative, a sequence of results which would tend to deny the presence of active rheumatoid arthritis. This interpretation was finally confirmed by the continued elevation of the serum uric acid and the appearance, after the sheep cell test had been negative for two months, of acute joints characteristic of a gouty reaction which responded to the administration of colchicine, sulfinpyrazone and phenylbutazone.

This is not to imply that the titre in definite cases of rheumatoid arthritis does not fall. Indeed, we have observed such cases and are very much interested in the association between the clinical picture and the rise and fall in the sheep cell titre in a long-term study. However, there is no doubt that the general picture in an established case of rheumatoid arthritis is that a positive test tends to persist within one tube in the dilution series for at least some months.

There still remain in this study group some 23 patients presenting with more or less nondescript and short-term illnesses in which the positive test suggests to us that the patient should indeed be followed up carefully. It is tempting to suggest that the likelihood of the development of rheumatoid arthritis is significantly greater in this group than in individuals with negative tests. Clearly, much more work is required in this area, and a number of these patients are being followed up at the present time on a long-term basis to evaluate this possibility. It is interesting to note that Hall, Mednis and Bayles,[7] in a study using the latex agglutination and inhibition techniques, reported in 1958 that 11 cases in this category subsequently developed overt rheumatoid arthritis. A further case was reported by Bloomfield[2] in which a patient with syphilis demonstrated a positive test in 1953 and in 1954 without any evidence of an arthritic disorder. The latex fixation test in 1958 was positive in a titre of 1280, and at that time the patient showed clinical evidence of overt rheumatoid arthritis. In our own hands two patients have been observed in whom the occurrence of a positive test preceded the development of overt rheumatoid arthritis by several months. Interestingly enough, one further patient who was initially suspected of having active syphilis, was found to have a persistently positive SSCA test and subsequently developed diffuse collagen disease in the form of dermatomyositis.

Although we would feel that a useful interpretation can be made of positive tests in groups of

patients presenting with rheumatic disorders, the same cannot be said with respect to the application of this test to mass populations as a survey tool. Here it seems likely that the incidence of positive tests in non-rheumatic disorders would be of such a magnitude and would require the clinical assessment of such a large group of individuals that its purpose would be defeated. The possibility of using this test to detect the development of rheumatoid arthritis in patients before any joint manifestations appear seems, at this stage, very unlikely, unless by further study it can be shown that there is, in fact, a macroglobulin that has characteristics which are specifically associated with rheumatoid arthritis.

Finally, it is also important to point out that a negative test does not definitely deny the diagnosis of rheumatoid arthritis. An initial negative test was recorded in 29 of the 217 patients in our group clinically diagnosed as definite rheumatoid arthritis. Clinically, the diagnosis hardly seems to be questionable in these cases, and this poses the problem as to whether seronegative patients constituted a group with features that differ from those of patients with positive reactions. A significant proportion of this group of patients represent cases of long-standing and "burnt out" disease, in whom one could postulate that perhaps the production of the rheumatoid factor, as in those cases of non-rheumatoid disease with positive tests, occurs only during the progression of the disease. It is possible, therefore, that prognostic significance may be attached to serial determinations of the SSCA test.

Previous work from this laboratory has indicated that the incidence of positive reactions and the height of the titre can be associated with the duration of the disease and with overall disease severity. The prognostic significance of a sheep cell test is being presently evaluated, and the groups of patients are being followed with serial determinations in an attempt to correlate the behaviour of the titre with the course of the disease. A preliminary survey of continuous two-year data which we now have available has so far revealed nothing more than a confirmation of the relationship between titre, duration of disease and overall disease severity. We have been able, however, to define certain distinctive patterns in our groups of patients and have been able to categorize them in a definite fashion. We would feel that a more detailed analysis and more extended observation is necessary to reveal the possible prognostic significance of the behaviour of the sheep cell titre with time, in rheumatoid arthritis.

SUMMARY

An evaluation of the diagnostic significance of the SSCA test has been carried out on a group of 1012 patients with various rheumatic disorders. Although a positive test is clearly not an exclusive feature of rheumatoid arthritis, individuals in whom this disease is established tend, as a group, to demonstrate positive tests more frequently, in higher titre and over a longer period of time than any other group.

A consideration of the titre and its fluctuation with time in the light of the clinical picture in the patient has been shown to allow a useful interpretation of the SSCA test.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE SURGICAL TREATMENT OF GALL-STONE DISEASE

Gall-stones are foreign bodies, and, other things being equal, they should be removed before infection and other complications occur, which increase the risks of operation and diminish the chances of permanent cure for the patient.

In reviewing four thousand operations which we have performed upon the gall-bladder and biliary passages (C. H. and W. J. Mayo, February 20, 1911), I have been impressed with the fact that the mortality was due to the complications incident to the disease, rather than to the removal of gall-stones from the otherwise normal gall-bladder. Not only is the mortality greatly increased by the involvement of the deep bile passages, the liver, pancreas, and neighbouring viscera, but the gall-bladder may also be found in such a condition as to render an attempt to save it impracticable and fraught with the possibility of a recurrence of symptoms. The gall-stones are, however, the responsible agents in the production of these complications, inasmuch as they set in motion a train of events which would not have occurred had the gall-stones been removed early in the history of the disease. —William J. Mayo (Rochester, Minn.), *Canad. M. A. J.*, 1: 866, 1911.

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THE POST-MYOCARDIAL INFARCTION SYNDROME: REPORT OF TWO CASES DEMONSTRATING A RECURRENT TENDENCY

SIDNEY A. CARLEN, M.D.,* *Toronto*

TRANSIENT pericarditis observed during the week after a myocardial infarction is a common phenomenon. Pericarditis of this type (pericarditis epistenocardia) is seen in 30%[1] to 80%[2] of postmortem specimens, and daily clinical examination will reveal a pericardial friction rub in about 20% of patients.[3] It does not occur before the second day and is rare after the sixth. Presumably, the accompanying friction rub indicates extensive and transmural infarction, smaller lesions being localized to the subendocardial or intramural areas. Pericardial effusion is uncommon, and its presence suggests hemorrhagic pericarditis aggravated by anticoagulant therapy, ventricular leak with tamponade, or an erroneous initial diagnosis.

A peculiar type of pericarditis appearing between the second and eleventh week after coronary occlusion was first reported by Dressler[4] in 1955. It has been called the post-myocardial infarction syndrome, and further observations[5, 6] have taught the clinician how to distinguish it from other complications such as pulmonary infarction, bronchopneumonia and recurrent myocardial infarction.

The syndrome is manifest at the onset by pericardial or pleural pain followed in a day or two by fever, persistent loud pericardial and/or pleural friction sounds, and signs of patchy pneumonitis. Radiographic study of the chest may indicate increased heart size due to pericardial effusion, single or bilateral pleural effusion, and basal pneumonic densities. The leukocyte count and sedimentation rate rise, the serum glutamic oxaloacetic transaminase level (SGOT) does not change and, in 50%[4] of instances, the electrocardiogram may show new RST-T segment elevations indicative of pericarditis appearing as a complication of myocardial infarction.[7]

When removed, the effusions are usually serosanguineous or less frequently serous. Cultures of pleural fluid and sputum are negative, and the inflammatory reaction is non-bacterial. Although the prognosis is good, recurrences are frequent for several months or longer. The response to adequate doses of corticosteroids (usually prednisone) is dramatic and diagnostic. There is a close resemblance to the so-called post-mitral commissurotomy syndrome.[8, 9] The latter, no longer considered to be a peculiarity of the postoperative rheumatic heart patient, is mimicked by a reactive inflammatory serositis and pneumonitis following 20% to 30% of operative procedures involving pericardiotomy in congenital and non-rheumatic heart disease.[10] Furthermore, an almost identical syndrome may follow accidental trauma to the pericardium, whether it be penetrating[11] or non-penetrating.[12] The post-pericardiotomy syndrome, post-myocardial infarction syndrome, and post-mitral commissurotomy syndrome show some common pathogenic features, particularly the presence of free blood or necrotic material in the pericardial sac. The delayed appearance of this syndrome, two weeks or longer after injury, and its prompt response to prednisone, suggest a hypersensitivity state dependent upon the production of autoantibodies.[13] Further proof of this mechanism is still required.

The clinical setting in which post-myocardial infarction syndrome occurs creates, in itself, diagnostic and therapeutic problems. Failure to diagnose it may initiate a program of treatment hazardous to the physical and psychological welfare of the patient. The two case presentations which follow exemplify some of these difficulties, and the tendency of the syndrome to recur.

CASE REPORTS

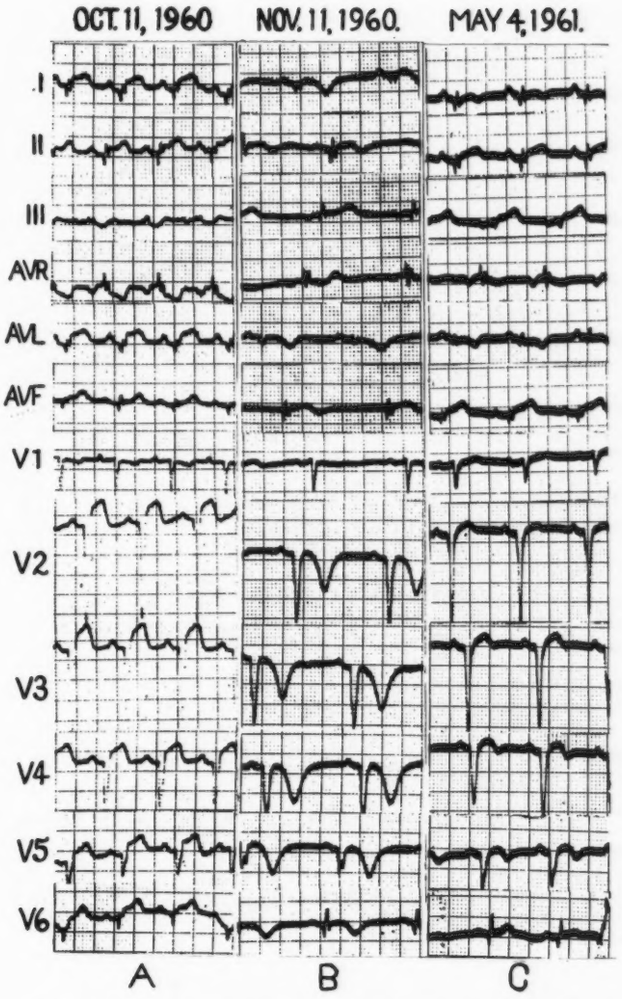
CASE 1.—I.S. (No. A63714). On October 9, 1960, while playing golf, a 45-year-old white male executive developed sudden, severe substernal pain radiating to the left pectoral area, shoulder and inner side of the left arm. Previously he had enjoyed good health except for a chronic, currently inactive duodenal ulcer. Previous electrocardiograms had been normal. The pain, somewhat rhythmic in nature at onset, eventually became extreme. On admission to the New Mount Sinai Hospital, Toronto, he was noted to be sweating, his blood pressure was 150/100 mm. Hg, his pulse 100 per minute and his temperature 99.4° F. The heart sounds were normal and the lungs were clear. An electrocardiogram indicated a recent, extensive anterior wall myocardial infarction. Characteristic pain persisted for one day.

On the third hospital day, the temperature was 102.8° F., pulse 105, blood pressure 98/68, and the pain had gradually decreased.

An electrocardiogram two days after admission showed extensive anterior wall myocardial infarction with a well-marked action current of injury or pericarditis, indicated by the ST segment elevations (Fig. 1A). On that day, a pericardial friction rub was heard, and the patient now complained of pain in the left pectoral area referred to the tip of the left shoulder and aggravated by breathing or coughing. This pain was considered to be pericardial in type. Heparin and bishydroxycoumarin (Dicumarol) therapy had been instituted on admission, the heparin being discontinued when a prothrombin time of 34 seconds, with a control of 14 seconds, was reached. Despite the history of duodenal ulcer, the severity of the myocardial infarction was considered sufficient to merit anticoagulant therapy. No occult blood appeared in the stools.

Laboratory results were as follows: SGOT readings on the first three days were 41, 550 and 119 units, respectively; his hemoglobin was 101%; erythrocyte

*Senior Attending Physician in Charge of Section of Cardiovascular Disease, Department of Medicine, New Mount Sinai Hospital, Toronto. Consultant (Hon.), Department of Medicine, Doctors' Hospital, Toronto.



Figs. 1 a, b, c.—(Case 1—I.S.) ECG (electrocardiogram) taken two days after attack shows extensive anterior wall myocardial infarction with marked ST-T elevations partly a result of pericarditis. ECG later and during first bout of syndrome shows persistent ST-T segment elevations. Recent record has low voltage and ST-T segment elevations—compatible with chronic pericarditis.

count 5.12 million per c.mm.; leukocyte count 10,900 per c.mm. with a differential count of neutrophils 50%, stab forms 21%, lymphocytes 13%, monocytes 15%, and eosinophils 1%. His sedimentation rate was 34 mm. in one hour (Westergren); blood sugar 93 mg. %; blood urea nitrogen 9.5 mg. %; and serum cholesterol 270 mg. %.

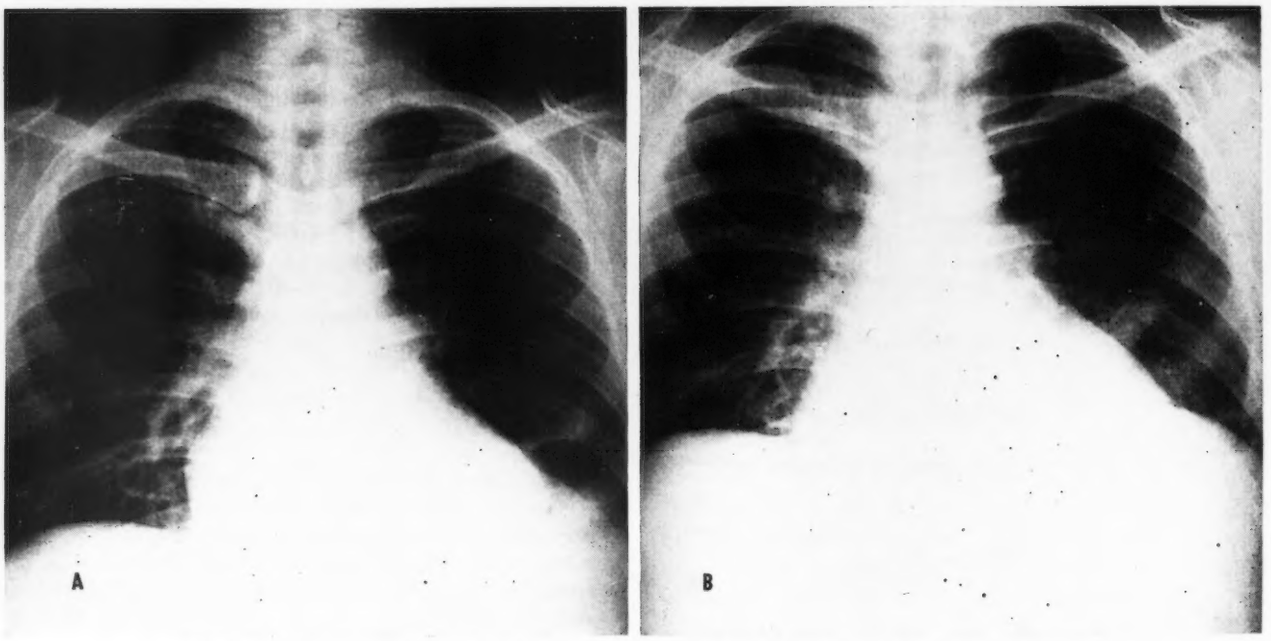
Pericardial pain was troublesome until the sixth day. On the tenth hospital day, the patient was comfortable with a blood pressure of 100/70 mm. Hg, temperature 98.6° F., and a pulse rate of 84 per minute. It was noted that the apex beat was displaced 1.5 cm. to the left of the midclavicular line and was slightly heaving. This was considered to be evidence of enlargement of the left ventricle. The heart sounds were normal.

On the 32nd hospital day, before attempting ambulation, the patient developed sharp left pectoral pain radiating to the left shoulder and aggravated by breathing or coughing. The electrocardiogram obtained at this time showed well-marked residua of the infarction, with persistent ST-T segment elevations (Fig. 1B). The temperature rose to 99.8° F.; the leukocyte count, which had previously dropped to 4000, increased to 10,000 per c.mm. with 71% neutrophils; the sedimentation rate, which had decreased to 22 mm., rose to 32 mm. per hour; two SGOT estimations were 40 and 44 units, respectively. A routine chest radiograph obtained prior to the new symptom had shown cardiac enlargement and some horizontal linear markings in the left costophrenic angle. Three days later, a repeat chest radiograph (Fig. 2A) showed consolidation in the left lower lobe with overlying pleural effusion. A provisional diagnosis of post-myocardial infarction syndrome was made, and prednisone, 30 mg. a day, was prescribed. Within 24 hours, all pain had cleared and the patient felt well. A chest roentgenogram (Fig 2B) obtained five days later showed marked clearing with residual haziness of the left diaphragm. The dose of prednisone was reduced gradually to 10 mg. a day until his discharge from hospital on December 1, 1960.

At home, therapy consisted of maintenance anticoagulation with bishydroxycoumarin (Dicumarol), prednisone and sedatives. He remained comfortable until January 1, 1961. At that time, during a recurrence of pericardial pain, a pericardial rub was heard; the lungs were clear. An electrocardiogram showed no new changes. The sedimentation rate was 30 mm. per hour, and the SGOT level was 32 units. Since this syndrome may be aggravated by the continued use of anticoagulants, bishydroxycoumarin was discontinued and the dose of prednisone was temporarily increased. There was immediate improvement, and the patient remained comfortable until February 15, 1961. On a maintenance dose of 10 mg. prednisone daily, he developed a severe recurrence of left chest pain. Examination at home revealed a pulse rate of 98 per minute, temperature 101.4° F., and a blood pressure of 115/80 mm. Hg. There was dullness and decreased air entry in the left base with distant bronchial breathing and a loud pericardial friction rub. He was admitted to hospital on February 19, 1961, for further observation. A chest roentgenogram (Fig. 2C) confirmed the presence of a small left basal consolidation with pleurisy. Cardiac enlargement was noted as before. An electrocardiogram showed further absorption in the area of infarction. Serial SGOT levels were 26, 17 and 22 units, respectively; urinalysis was negative with a specific gravity of 1.017; his hemoglobin was 89%; erythrocyte count 4,560,000 per c.mm.; leukocyte count 8300 per c.mm., with a differential count of neutrophils 68%, stab forms 10%, lymphocytes 18%, and monocytes 4%; his sedimentation rate was 35 mm. in one hour; and his hematocrit was 45%. The daily dose of prednisone was increased to 30 mg., and within two days his symptoms cleared. A follow-up chest radiograph five days later showed almost complete clearing.

On March 1, 1961, the patient was discharged with no chest findings and a sedimentation rate of 23 mm. per hour. Since then he has been on a daily maintenance dose of 10 mg. of prednisone. Periodically there has been fleeting pericardial pain but no important recurrence. He does not suffer from angina pectoris or dyspnea. The most recent electrocardiogram (Fig. 1C), on May 4, 1961, showed a fairly well stabilized, extensive anterior wall infarction, persistent ST-T segment elevations and low voltage in the limb leads. Fluoroscopy of the chest revealed a rather quiet heart with moderate diffuse enlargement. The present status is suggestive of a chronic pericarditis, possibly with a small effusion.

Summary.—Following a most severe anterior wall myocardial infarction, post-myocardial infarction



Figs. 4 a, b.—(Case 2—F.S.) Radiograph of chest during initial attack of post-myocardial infarction syndrome shows left pleural effusion, streaky densities in both lower lung fields, and enlarged heart shadow. Spontaneous clearing is seen two weeks later with persistent cardiac enlargement. Eight months later fluoroscopy showed normal heart size.

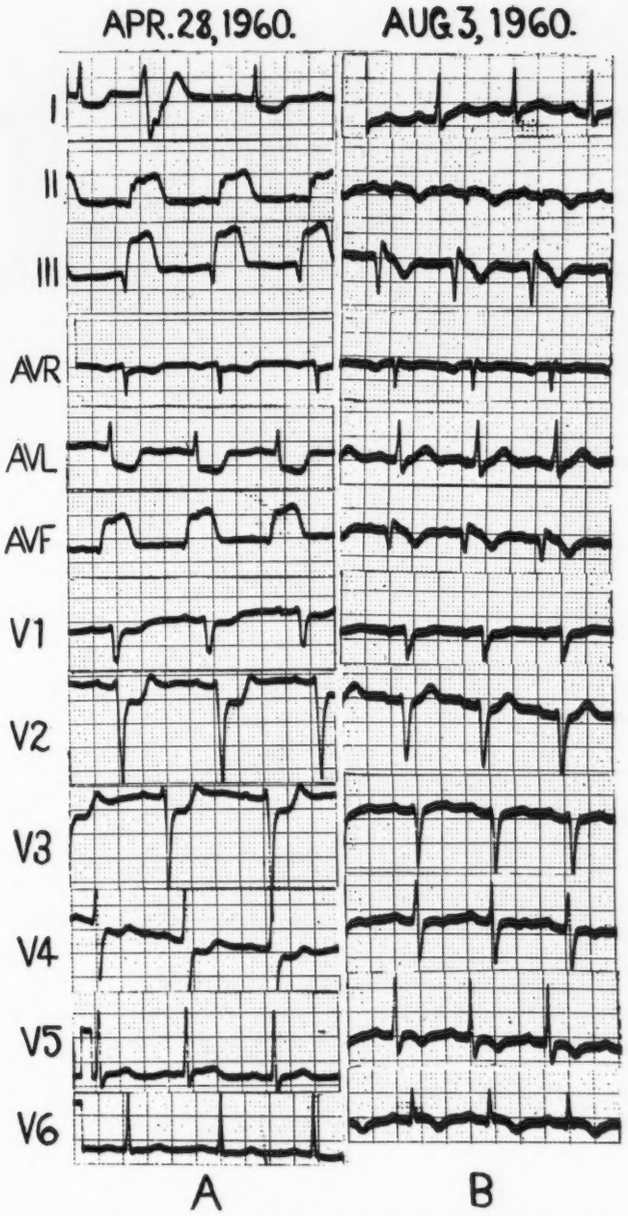
syndrome recurred during the following 5th, 12th and 18th weeks. Prednisone therapy was reliable, and it seemed that discontinuance of anticoagulants was not the critical factor. The patient still presented evidence of chronic pericarditis seven months after his attack.

CASE 2.—F.S. (No. 69898). On April 26, 1960, this 36-year-old, white male bartender developed severe crushing midsternal pain radiating across the chest to both shoulders and arms. This pain persisted, requiring repeated injections of morphine for relief. On admission (Doctors' Hospital, Toronto) the blood pressure was 160/130 mm. Hg (falling within 24 hours to 110/80), pulse 100 per minute, temperature 99.9° F.; the lungs were clear, and the heart sounds were normal. For several months prior to this illness, he had noted substernal discomfort induced by effort and relieved by rest. The laboratory findings were as follows: His Hb. was 15.9 g. %; leukocyte count 8000 per c.mm. with a differential count of neutrophils 69%, stab forms 6%, lymphocytes 33% and monocytes 2%; his blood smear appeared normal; the sedimentation rate was 24 mm. in one hour; SGOT 110 units; blood sugar 84 mg. %; and NPN 30 mg. %. Two days after admission the sedimentation rate was 59 mm. per hour, the leukocyte count was 15,600 per c.mm., the serum cholesterol 205 mg. % and the electrolytes were normal. The electrocardiogram showed a recent, extensive posterolateral myocardial infarction (Fig. 3A).

Anticoagulant therapy with bishydroxycoumarin (Dicumarol) was instituted on admission. The temperature reached 102° F. on the third day and remained elevated for five days with gradual defervescence. During this period, bilateral crepitant rales appeared, the pulse rose to 120 per minute, and slight neck vein distension was apparent. He was given diuretic therapy, and all signs of failure cleared rapidly. During the first week, a loud pericardial friction rub was heard, which was not present after the seventh day. Simultaneously he noted precordial pain radiating to the left shoulder tip, aggravated by respiration or movement. Subsequently, the hospital course was uneventful but prolonged because of the extent of myocardial involvement. At the time of his discharge, on June 16, 1960, he was comfortable on maintenance bishydroxycoumarin therapy and salt restriction.

The author did not see the patient again until August 3, 1960. In the interim he had been hospitalized elsewhere for a period of four weeks, and had been discharged four days before. Shortly before this hospitalization, he had developed severe left chest and precordial pain radiating to the left shoulder and aggravated by breathing. This was followed by a spiking fever of 102° F. and a non-productive cough. In hospital a diagnosis of either pulmonary infarction or left bronchopneumonia had been made, and he received antibiotics for the most part of a month. However, his response to this therapy was negligible, and he continued to have pain, sweating and fever. Eventually, his symptoms improved, and he was discharged on maintenance bishydroxycoumarin therapy. Two serial radiographs of the chest obtained during this hospitalization are shown in Figs. 4A and 4B. The first shows an enlarged heart with globular prominence of the left ventricle and haziness of the left diaphragm suggesting a small pleural effusion. There are patchy linear densities in both right and left lower lobes. The second film taken two weeks later shows clear lung fields. SGOT estimations had never exceeded normal levels during this time.

Office examination revealed that his weight was 152 lb., his blood pressure 120/80 mm. Hg, and his pulse 100 per minute. The lungs were clear, the heart sounds normal and there were no signs of congestive failure. Fluoroscopic examination indicated moderate prominence of the left ventricular salient, and the electrocardiogram (Fig. 3B) showed residua of previous posterolateral infarction with persistent ST segment elevations in leads 2, 3, AVF and V6.



Figs. 3 a, b.—(Case 2—F.S.) ECG obtained shortly after attack reveals severe basal infarction and marked ST-T segment changes. Three months later, persistent ST-T segment elevations are noted.

As it was suspected that the patient had suffered a post-myocardial infarction syndrome, bishydroxycoumarin was discontinued, and no specific therapy given. On a regimen of rest and salt restriction, the patient remained comfortable until October 13, 1960, at which time he developed left chest pain followed the next day by a temperature of 100° F., chilly sensations and slight cough. Examination revealed a pericardial friction sound and fine rales in the left axilla. Fluoroscopy was essentially unchanged. The electrocardiogram showed no alterations from the previous record. A presumptive diagnosis of post-myocardial infarction syndrome was made, and prednisone 30 mg. a day was prescribed. Within 24 hours, the patient reported complete freedom from all symptoms. The dose of prednisone was reduced, to be discontinued three weeks later. In January 1961, a similar, milder recurrence appeared, to be relieved immediately by prednisone. Since that time the patient has been well and has returned to his job as a bartender. The most recent electrocardiogram of April 10, 1961, was unchanged. Since fluoroscopy now indicates normal heart size, it is suspected that previous cardiac enlargement was a result of pericardial effusion rather than of cardiac dilatation.

Summary.—A young man who suffered a severe posterolateral myocardial infarction with pericarditis did well until a post-myocardial infarction syndrome developed 10 weeks after the attack. Unrecognized and untreated, the syndrome cleared spontaneously in four weeks. Two further episodes appeared after discontinuance of anticoagulant therapy, viz six and eight months after the original myocardial infarction. These responded well to prednisone therapy.

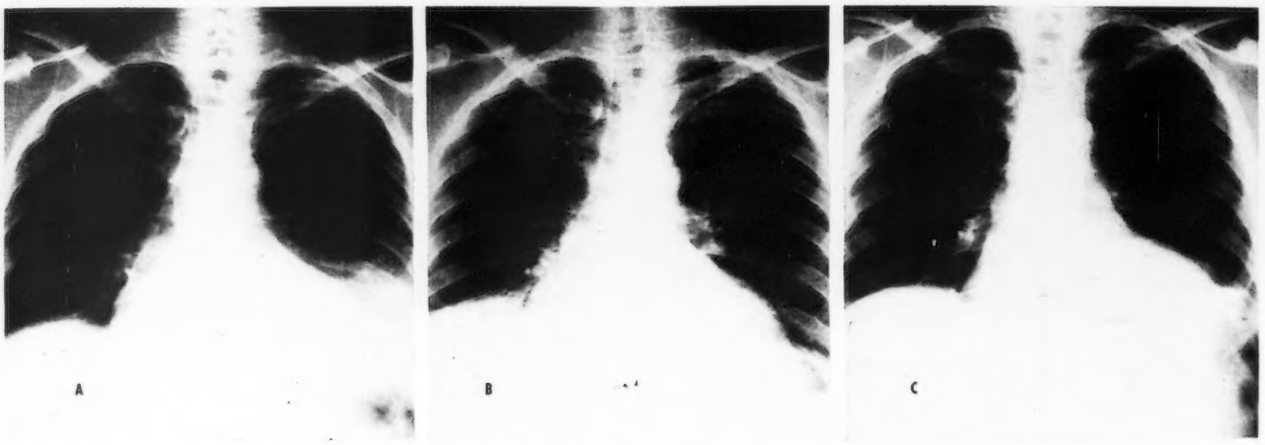
DISCUSSION

Both patients described in this report suffered severe myocardial infarctions and showed pericarditis epistenocardia. Similarly, the majority of Dressler's cases had had severe infarctions with pericardial symptoms or signs during the first week. This suggests that the more severe the initial pericardial insult, the more liable is the patient to develop the post-myocardial infarction syndrome. The latter syndrome follows about 3% of myocardial infarctions and, unfortunately, is most prevalent in the severe case in which the physician fears late embolic or myocardial complications. For example, the increased cardiac shadow caused by pericardial effusion may be misinterpreted as cardiac dilatation or ventricular aneurysm. Pulmonary consolidation and pleural rubs may suggest pulmonary infarction, bronchopneumonia, or congestive failure. In Case 2 the missed diagnosis resulted in an unnecessary, prolonged, second hospitalization.

The recurrent nature of the syndrome is well illustrated in both patients. Case 1 showed three recurrences in five months and still has evidence of chronic pericarditis with a need for maintenance prednisone therapy. Case 2 had three recurrences, the last appearing at the eighth month. If these recurrences are misdiagnosed as new coronary thromboses — and likely many have been in the past — unintentional psychologic crippling may result.

Although both patients developed the syndrome initially while on anticoagulant therapy, subsequent recurrences appeared after its cessation. However, Dressler's advice to discontinue anticoagulants appears sound, since he has reported one patient who died as a result of hemorrhagic pericardial tamponade. In most cases, the syndrome occurs late in the illness, at which time the protective action of anticoagulants is not so urgently required. Certainly long-term anticoagulant therapy is a hazardous program for such patients.

The post-myocardial infarction syndrome may be distinguished from extension of myocardial infarc-



Figs. 2 a, b, c.—(Case 1—I.S.) Radiographs of chest showing consolidation of left lower lobe, left pleural effusion and cardiac enlargement. Five days later almost complete clearing appeared on prednisone therapy. The film on the right (Fig. 2c) shows a late recurrence with patchy consolidation and pleurisy on the left side.

tion by the pleuropericardial type of pain, absence of characteristic electrocardiographic changes, and normal SGOT. Pulmonary infarction may be ruled out by the concomitant pericarditis, and pulmonary infection by the lack of evidence of bacterial invaders. Antibiotics are useless, and prednisone therapy in adequate doses (20-40 mg. per day) will often resolve a diagnostic riddle within 24 to 36 hours.

SUMMARY

Two cases of post-myocardial infarction syndrome have been presented. Both patients demonstrate the recurrent nature of this illness up to and beyond six months after myocardial infarction.

The diagnostic procedures have been discussed, particular stress being placed upon the importance of the physician's awareness of its possible presence and the value of a therapeutic trial with prednisone.

The syndrome resembles the reactive state which may follow surgical or non-surgical trauma to the pericardial sac and may be the result of an autoimmune reaction.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Men of great ability have continued to work in the hospitals for a variety of reasons, which have been diminishing in force and will no longer hold good when patients can demand as a right what was formerly received as an act of charity. Physicians who could achieve fame in the hospitals alone, now shape their careers in the laboratory. The hospital bedside is no longer the only resort for clinical experience, and the wisest physician is not always the one who sees the most cases. A scientific training is now more important than ever before and the routine of the hospital less alluring.

And if the people pay by compulsion for their treatment, charitable persons will be disposed to allow the support of hospitals to come from the public funds. There will then be fewer of these institutions, and the spirit of charity will be replaced by a cold, official atmosphere which is not congenial to a member of a free profession. When the higher lights disappear from the wards and operating rooms, students will vanish; and without the stimulus which the presence of students creates, institutions for the care of the sick will resemble a house of detention instead of a place of hope and cure.

A physician succeeds in virtue of a humane nature, because in the treatment of the sick there is large room for those qualities of the heart which are too precious to be appraised by an official superior. When physicians become civil servants, those who are peculiarly adapted for healing the sick will be automatically forced out of the service and into private practice, where their gifts will be more highly appreciated. The rich will be the gainers and the last state of the poor will be worse than the first.—Excerpt from editorial, *Canad. M. A. J.*, 1: 887, 1911.

SPECIAL ARTICLE

BRITISH COLUMBIA MENTAL HEALTH SERVICES: HISTORICAL PERSPECTIVE TO 1961*

RICHARD G. FOULKES, B.A., M.D.,†
Essondale, B.C.

INTRODUCTION

THE Provincial Mental Health Services (P.M.H.S.) of British Columbia embrace a number of institutions utilizing buildings of various styles of architecture representative of the nine decades during which they have developed. All are under the control of a Deputy Minister, Dr. A. E. Davidson at the present time, who reports from his headquarters in Vancouver to the Minister of Health and Hospital Insurance, the Honourable Mr. Eric Martin, in the capital city of Victoria.

At the end of the 1959-1960 fiscal year, the last for which data had been published at the time of preparation of this paper, the constituent parts of the Provincial Mental Health Services were located in a number of areas of the province, with maximum concentration at Essondale, a 1000-acre site in the Fraser Valley, near Port Coquitlam, 25 miles to the east of Vancouver. Other units were at nearby locations on the lower mainland, in the interior, and on Vancouver Island.

The elaborately landscaped grounds at Essondale are the site of the three huge four-storied buildings of the Provincial Mental Hospital. These buildings, constructed of red brick with white colonades and multitudinous small panes of glass surrounded by steel sash, housed on March 31, 1960, some 3019 patients. In the same area are the Crease Clinic of Psychological Medicine, housing some 265 patients in a brick structure of more recent design; the "Homes for the Aged", sheltering 657 in a collection of buildings that vary from frame "Tudor" to reinforced concrete "Contemporary"; a Nurses Training School with new, modern, functional units; and a large and productive colony farm.

On well-kept grounds at New Westminster, 12 miles to the west and half way between Essondale and Vancouver, stand the assorted buildings of Woodlands School. These vary from structures of stone and wood that possess remnants dating back to the 1890's, to those of new construction that rival in appearance any building in the area. At the close of the 1959-1960 fiscal year, the units of this institution provided quarters for 1387 mental defectives. Nearby, in South Burnaby, almost at the half-way point between New Westminster and Vancouver on the Grandview Highway, are the modern buildings of the Mental Health Centre.

On Vancouver Island at Saanich, not far from Victoria, Colquitz Mental Hospital, a converted prison — with grey stone walls, ramparts, and bars —houses 288 patients. In the interior of the province, two renovated Second World War military hospitals, one at Terrace and the other at Vernon, provide housing for 288 and 284 aged persons respectively, and at Tranquille, near Kamloops, a surplus tuberculosis sanatorium was "home" to 109 ambulant mental defectives, the first of a large number to be transferred from Woodlands School.

In 1959-1960, the institutions of the P.M.H.S. provided accommodation for a total of 6247 patients of all types. At the same time, the total number of persons under treatment was 10,362; the gross cost of the operations was in excess of 14 million dollars, and the staff numbered 2927, exclusive of more than 300 students.

The development of this organization from meagre beginnings in 1872 was thought to be worthy of a review at this time. As a consequence, this essay was prepared after study of the original "Case Books", the Mental Health Services' annual reports, pertinent Royal Commission proceedings, and the published reports of other investigative groups, such as the 1951 report of the American Psychiatric Association.

THE COLONIAL PERIOD TO 1871

During the colonial period of the history of British Columbia, the only facility available for the mentally ill was the common gaol. John Robson, then editor of *The British Columbian*, later Provincial Secretary and Premier of the Province, described in an editorial entitled "A Voice from the Dungeon", their custody in the New Westminster Gaol on July 23, 1863. "The cells in which they [the lunatics] are confined are not at all adapted for such a purpose, entirely too small, ill ventilated, unheated and an offensive effluvia arising from beneath them, the result of no proper system of drainage."

In the older colony of Vancouver Island, conditions were no less foul in the Victoria "lock-up", where Dr. J. S. Helmcken, British Columbia's first physician, saw the colony's earliest mental patients as far back as the early 1850's.

The facilities of Napay Asylum in San Francisco were also used occasionally, particularly for the committal of those insane members of the horde that travelled from this centre to Victoria en route to the gold fields of the Cariboo in 1858 and 1859.

THE ASYLUM—1872-1901

When female patients began to present themselves, the gaol became even more unsuitable. After an abortive attempt to house "lunatics" of this sex

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†Resident physician, Provincial Mental Hospital, Essondale, B.C.

in a private home on Pandora Avenue in Victoria, the first asylum was established.

This was a "modest building" constructed of wood, 50 by 40 feet, that contained a number of "cells" or small single rooms. It was formerly the Royal Hospital, a pest house, and was located on the Songhees Indian Reserve in Victoria Harbour adjacent to the Marine Hospital. It accepted its first patient, a young woman referred by Dr. Helmcken, on October 12, 1872, just 14 months after B.C.'s entry into Confederation. At the end of this first day of operation, the asylum was occupied by seven patients, all transferred from the "lock-up". To look after these were an equal number of staff, including a Dr. Powell, the Medical Superintendent, and Mrs. Flora Ross, Matron. An "Insane Asylum Act" was promulgated the following year.

Within the next five years, in spite of the addition of a small wing, the facilities became inadequate and a second asylum, built at the cost of $24,000, was constructed as a replacement at New Westminster on the present site of Woodlands School. This new unit with a population of some 37 patients was opened in 1878.

The first annual report was not published until the year 1882. This document shows that the resident population had climbed to 49 and that the institution was under a lay Superintendent, Mr. James Phillips, with a Medical Officer, R. I. Bently, M.B., B.S.

The first New Westminster Asylum is described as an ugly building with windows so high that the outside could be seen only by standing on a table. Further, it was poorly heated by means of open grates and so overcrowded that two patients were compelled to share a single room. The following year some improvements were made to the buildings, and in 1885 the asylum was, once more, headed by a physician, Dr. Bently. Mr. Phillips henceforth held the position of steward. This year was, in addition, the first in which patients were allowed to work. The therapeutic effect on at least one of them is noted by Dr. Bently in the large, heavy, leather-bound case book that was the means of recording case histories in that day. We gather that improvement in a male patient, discharged "cured" on March 12, 1885, ". . . dated from the time he commenced to go out steadily to work every day".

During this early period that continued to the enforced retirement of Dr. Bently in 1895 as a result of a Royal Commission inquiry the previous year, custodial care only was all that could be provided, with a minimum of recreation and outside work. The only physician, embattled with the problem of keeping the per diem cost at a low level (it was 48¼c per day in 1891), of urging construction to house the increasing patient population, of ensuring adequate water supplies, and of visiting the Royal Columbian Hospital sometimes twice a day in addition to writing his own letters, had little time for experiment, therapy or supervision.

The cruelty of the "keepers" during this period was scandalous. As was stated in the report of the Royal Commission, composed of Drs. Hasell and Newcombe of Victoria, methods were in use that had been discarded in Great Britain more than a generation before. Equipment such as handcuffs, leather mitts, pinion straps, camisoles, and straight jackets, with the cruel rope halter called "the Martingale" that could be used as a strangulation device, were in almost daily use. Also applied were tortures such as the "dip", in which a patient, arms handcuffed behind his back, was plunged head-down into a tub of cold water until he very nearly drowned, and "the cage", a box constructed of wooden slats and made only large enough for a human body in which a patient might be kept confined for many hours.

In 1895, Dr. Boddington assumed the senior position. The attendants who had been implicated in the grisly affairs of the last régime, were forced to resign.

During the next few years, Dr. Boddington addressed himself to the task of humanizing the institution — adding pictures to the walls, urging landscaping of the grounds, and reducing physical restraint. In addition, he improved the food, constructed a much needed operating room, badgered the government of the day for increased maintenance funds, and started on a policy of the deportation of aliens who made up 70% of population in residence. On one occasion, he personally escorted to England a party of 22 "half-witted ne-er-do-weels", the progeny of wealthy British families who had been sent to the Colonies as punishment for their failure to adjust to their parent country. Upon his return, he began formulating plans for the return of the Chinese, a large alien group that had given concern for many years.

In 1897, "The Provincial Asylum" was re-named "The Public Hospital for the Insane (P.H.I.)" and a new act was promulgated incorporating within it an "Urgency Order" that had long been required.

In 1901, a Royal Commission, composed of Dr. C. K. Clarke, Medical Superintendent of the Rockwood Asylum, Kingston, Ontario, inquired into the operation of the institution. In spite of containing praise of the minimal restraint, good food, and the excellence of the new surgical ward, Dr. Clarke's report criticized the "excess staff" and the high wages that they were paid, and recommended stricter economy, better bookkeeping (the old register was still the only record of the patient and slates were in use for passing messages from one nursing shift to another), further brightening of the wards, improved facilities for outdoor exercise, the establishment of a School for Nurses, and a Colony Farm.

As it was apparent that to bring about the required changes would entail an increased amount of work, Dr. Boddington "felt constrained through the advance of his years to relinquish the labour to younger hands'".

"MORAL TREATMENT" 1902-1912

These were the words of Dr. G. H. Manchester, who stated with optimism in the 1902 annual report that the institution ". . . has entered upon a new century under new management, and moreover has emerged from comparative insignificance and obscurity to become the largest . . . institution under the care and support of the Province of British Columbia."

The annual report, for the first time, contained a table of diagnoses (mania, melancholia, dementia, and paranoia). Until this issue, the patient had been described but rarely labelled. Noteworthy is the fact that *general paresis* formed 12% of the total number of admissions for the year (14 patients of a total of 115). In addition, an "open-door" ward was reported and a statement of treatment principles was given that officially introduced the era of "Moral Treatment". These principles were listed as (1) essential medicines, (2) good food (there was a shortage though, each patient, for example, being allowed only one egg per year and that at Easter), (3) regularity of living habits, (4) employment, (5) amusement, and (6) recreation. A need for separate facilities to deal with acute cases, the mental defective, the tuberculous patient and the "criminally insane" was recognized and a need for musical therapy and industrial training was discerned.

During his last year in office, 1904, Dr. Manchester wrote into the annual report the Kraepelin system of nomenclature. He announced, also, that the Government had purchased 1000 acres of land about 12 miles distant from P.H.I., near the junction of the Coquitlam and the Fraser Rivers, for purposes of expanding the mental hospital facility.

With C. E. Doherty, M.D., Dr. Manchester's successor, and Dr. Henry Esson Young, Provincial Secretary, the Hospital for the Insane at New Westminster saw the full development of the principles of the "moral treatment of insanity".

In addition to being the first year of Dr. Doherty's long tenure, 1905 marked the beginning of clearing of land for a Colony Farm. Upon admission, patients were segregated into "incurable", "curable", "feeble" and "infirm". Rest, work and amusement "judiciously selected" were basic treatment. A musical director was appointed, a Mr. Darcey, who organized an orchestra of institution employees.

Work was departmentalized and the "hospital" atmosphere heightened by using the word "nurses" rather than "keepers" or "attendants", and an attitude of kindness towards the patient was enforced by dismissal, if necessary.

With regard to therapy, none were denied exercise and fresh air, "Patients," Doherty wrote, ". . . walk the grounds by the hundreds." Medical treatment, work of all kinds in the shop or on the farm, and recreation, were individualized and had such effect that Doherty, in 1907, could make the claim that mechanical restraint of all kinds had been abolished. After the introduction of hydrotherapy techniques to calm the few disturbed patients who remained, he added that "chemical restraint", also, was no longer in use.

The contemporary method of recording case histories was established and all physicians' notes were typewritten from 1908. The same year, a laboratory was established, with its work done by Mr. E. P. Hughes, a competent bacteriologist, and, for the first time, research was added to the function of the institution. Detailed postmortem examinations were carried out on all for whom permission could be obtained, investigations into the spirochetal etiology of general paresis were pursued, and thousands of observations of blood and urine were recorded and correlated with the mental diagnosis.

By the end of 1912, in spite of serious overcrowding, there was reason for optimism. Crops raised on Colony Farm exceeded the most sanguine expectations and the "'Farmer's Advocate" of December 1912 described it as possessing ". . . the best equipped barns, stables, dairy equipment, and yards in Canada, if not the Continent." Dr. Doherty read papers before the B.C. Medical Society and at the 68th Annual Meeting of the American Medico-Psychological Association at Atlantic City, propounding his views of the treatment of mental illness, for which he received approbation from many sources.

The plans for the new hospital at Coquitlam, obtained by staging a competition between the architects of the province, received the highest commendation from psychiatrists in Eastern Canada and from the Lunacy Commission of New York State. They called for the building, in stages, of a number of structures, each specialized as to function: an administration building, an acute building, sick and infirm buildings, an epilepsy building, a pair of chronic buildings, and adequate living quarters for nurses. It was decided that one of the chronic buildings should be constructed first so that it could be used to house the overflow from the P.H.I., and the building now known as West Lawn was begun. The first building on the new grounds, named Essondale after Dr. Henry Esson Young, the Provincial Secretary, was opened on April 1, 1913. Two institutions were now in existence: the P.H.I. at New Westminster with Drs. J. S. McKay and H. S. Steeves, and Essondale with Dr. Freeze as Assistant Medical Superintendent. Dr. Doherty was Medical Superintendent of each.

During the 1914-1918 World War, the dual institutions began to have increasing difficulties. Many of the nursing staff and Dr. Doherty himself left to join the armed forces. Mr. Hughes, upon whom the function of the laboratory depended, died late in 1913 and could not be replaced for 14 months.

During Doherty's absence, the annual reports were edited by Dr. J. S. McKay who, continuing in the same vein as his superior, pressed for further buildings at Essondale, the new building already

being overcrowded, and advocated the reporting of known cases of *syphilis*, now known to be the cause of 12% of admissions. He also requested training for the 43 mental defectives then in residence and amendment of the "Mental Hospitals Act" to cover voluntary admissions.

In 1919, a six-year-old prison at Saanich on Vancouver Island was taken over to house "the criminally insane". The same year, Dr. McKay resigned and started the Hollywood Sanitorium in New Westminster (70 beds), the only fully recognized private treatment centre for mental disease that the Province was to see until psychiatric wards were established at the Vancouver General Hospital (40 beds), and the Royal Jubilee Hospital in Victoria (24 beds).

Dr. Doherty died on August 14, 1920. An era had passed, and it would be more than 30 years before the same feeling of optimism would again pervade the institutions.

RETURN TO CUSTODIAL CARE, 1912-1950

Dr. Doherty was succeeded by Dr. H. C. Steeves, who died on December 7, 1926, and was succeeded in turn by Dr. A. L. Crease, who continued as head of the organization until March 31, 1950.

During the 38-year period between the opening of the first building at Essondale and the resurgence of activity highlighted by the establishment of the Crease Clinic of Psychological Medicine, progress was slow and sporadic, and regression in some aspects of patient care took place.

Each of the buildings added during this interval, before they were officially opened, were doomed to become the site of suffocating overcrowding at an estimated average of more than 55% in excess of rated capacity. The resident population at the end of each 10-year period during this interval increased by approximately 1000. In 1912, it was 722; in 1924, when the first "acute building" now known as Centre Lawn was opened, it had risen to 1784; in 1930 when East Lawn was opened for women, 2411. By 1951, the number resident at the end of the year was 4602.

During this period, wards overflowed into the attics and basements, choking out areas needed for day use and therapy, especially for that of the occupational and recreational variety. On the wards, conditions were such that, towards the end of the period, there were more patients than beds. Those unfortunate enough to be in excess had to sleep on mattresses placed on the floor. Furthermore, a return to locked wards and even to physical restraint took place. As many as 30 patients in restraint and 51 in seclusion, mostly women, were counted by an inspection team as late as 1951.

Efforts to provide well-trained professional staff during this period moved forward when in 1925 a Miss Van Wyck, a registered nurse, became "Superintendent of Nurses", the first with this qualification to hold this important executive position. An "Instructress of Nurses", a Miss M. Mallott, was appointed in 1930, and the first Nurses Training School was established. June 1932 saw the first graduation exercises, addressed, appropriately, by Dr. H. Esson Young, then Provincial Health Officer. The first male graduates did not appear until 1940, and then were only five in number.

The Nursing Services, built up by 1938 to an enviable ratio of two registered nurses to one psychiatric nurse and one student, were devastated by the war. In 1942, the sudden resignation of 41 trained (most of the R.N.'s) and 72 partially trained staff reversed this ratio and resulted in the hiring of aides ". . . of various standards". At this point 56.5% new staff was devoid of any experience in hospital work or psychiatric training.

A change in hiring policy, in 1944, brought married women, mostly psychiatric nurses, back to the staff and relieved the situation. By 1945, male training, discontinued in 1940, was resumed and by 1947 the nursing problem had been stabilized but with a new ratio of 18 registered nurses, 44 psychiatric graduates, and 192 nurses-in-training.

The solution to the problem of providing separate facilities for the acute mental patient, the mentally defective, and the tuberculous had to await the 1950 period, but some changes were made that ameliorated conditions and assisted in "setting the stage".

With regard to the mentally defective, an effort, inadequate from the outset, to establish a school was made at Essondale in 1920. Dr. Steeves, in 1922, was the first to suggest using the P.H.I. for this purpose. This suggestion was underlined by the Royal Commission of 1925 that dealt in great detail with mental deficiency and sounded the keynote for the future that the problem was ". . . educational rather than medical". The number of mental defectives increased through the years. In 1927, they numbered 200; by 1930, 400. The transfer to P.H.I. started in 1932, and was near completion with five school teachers on staff when the "Schools for Mental Defectives Act" came into being in 1953.

Similar temporary measures were effected with the tuberculous patients. The first attempts at isolation in 1938 was unsuccessful, as these patients were placed on wards with patients suffering from other illnesses.

In 1940, two separate wards, one for each sex, were formed and were soon crowded with a total of 300 patients, 200 of whom were classified as "active".

Facilities for the care of the acute mentally ill remained inadequate because of overcrowding, although a psychopathic ward was established in the Centre Lawn building in 1924, with facilities that were improved when compared to those that had existed for many years. The Royal Commission as of 1925 recommended the construction of a separate institution, a "psychopathic hospital", as was in existence in the eastern United States, but this was not to come into being until the Crease Clinic of

Psychological Medicine with its 300 beds was constructed in 1948, by adding a wing to the recently vacated Veterans' Building built 13 years before.

Special provision for the aged psychotic became available in 1936, when the buildings of the Boys' Industrial School, abandoned in favour of the Borstal system and located on property adjacent to Essondale, were utilized as "Homes for the Aged". This collection of two-storey buildings, architecturally resembling Tudor style, and constructed on the side of a large hill, were obviously unsuitable for elderly patients but, nevertheless, fulfilled a need.

Various departments were formed during this period that, although each suffered from severe limitations, were available when resurgence occurred. Directors were found for occupational therapy and recreational therapy. Physicians on staff were appointed to direct or to work in major departments such as pathology, radiology, and pharmacy, but held these positions as duties secondary to their ward work, so that activity in one field was detrimental to effort in the other. A study of the reports on the laboratory, for example, reveals a variable load, usually contingent on the presence or absence of a laboratory technician, as well as the freedom of the medical officer in charge. A successful attempt was made to keep up with the admission serology tests and the routine examination of water and food, but routine blood and urine examinations fluctuated, as did the number of autopsies performed. The chief cause of death for many years is given in the reports as "exhaustion, due to . . .", followed by the psychiatric diagnosis. This diagnosis was most frequent in years such as 1931, when only one autopsy was performed on 304 deaths, and least in years like 1937, when 51 autopsies were carried out on 236 deaths.

A Social Service Department was established in 1932 with the appointment of Miss J. Killburn, R.N., a trained social worker. This action was based on a recommendation made by Dr. Steeves in 1926. This constantly understaffed group carried a large work load that was composed of case work done not only for the Mental Hospitals but also for the Child Guidance Clinic established in Vancouver on July 15, 1932, and later expanded to include Victoria (1934) and the travelling clinics to Nanaimo and Chilliwack (1935). The department also administered psychometric tests to various groups, including the Borstal Home candidates, and accepted responsibilities to lecture to classes at the University of British Columbia. All members of this department were responsible to the Welfare Branch until 1957, when they were transferred to the Department of the Provincial Secretary.

A psychologist, Mr. Watson, M.A., was appointed in 1937, thereby relieving the social work department of much of the labour expended in administering psychometric tests.

There were definite advances in treatment during this period, but limitations of staff and space reduced the number of patients to whom many of these could give benefit. By 1926, intravenous trypanarsamide had been used for syphilis and had been found to be effective but palliative only for general paresis. During this year, malarial therapy was begun and, by 1938, G.P.I. showed a definite decrease in frequency. By 1946, with bismuth, sulfonamides and penicillin added to the therapeutic agents, treatment was definitive. The purely physical treatments were less dramatic but gave rise to much optimism. Hydrotherapy, the chief physical treatment in the 1907 period, continued in use to the 1950's. The use of insulin shock was first reported as being carried out on 20 patients at a time, in the 1938 report. At this time pentylenetetrazol (Metrazol) therapy was introduced but was not too promising from the beginning. In 1940 (to provide an idea of the number affected) there were 239 patients on insulin shock and 301 on pentylenetetrazol; that is, 540 patients under treatment out of a total population of 3836. Insulin treatment was decreased during the war years, owing to the lack of trained staff. At the same time, electroconvulsive therapy came into use and replaced the dangerous and much hated pentylenetetrazol. Surgery for mental illness was introduced in 1946, when nine lobotomies were performed in the Vancouver General Hospital by Dr. F. Turnbull. The following year, there were 45 cases, and over the next five years psycho-surgery suffered a gradual loss of popularity as other means of therapy became available.

RENAISSANCE, 1950

March 31, 1950, was the last day of the 35-year career in the P.M.H.S. of Dr. A. L. Crease. It also marked the beginning of a new phase in the treatment of mental illness in the province. By this date, in addition to the departments of pathology, pharmacy, social work, psychology, occupational therapy, and recreational therapy that had been formed over the previous three decades and were now in charge of specialists, there was added a department of neurology. In addition, there came into being a new facility for the aged at Vernon, "The New Vista"—a rehabilitation centre for discharged female patients, and the Crease Clinic, ". . . dedicated to the intensive treatment and rehabilitation of the acutely ill and to education and research."

When Dr. A. M. Gee, Dr. Crease's successor, accepted on April 1, 1950, the senior position in the Mental Health Services, the population in residence was 4602. On this date, the various mental health activities were amalgamated into the Provincial Mental Health Services. Divisions were formed, governed by a "Hospital Council". These divisions were to be called: (1) The Active Treatment Services, (2) Geriatrics Division, (3) Preventive Services, (4) Rehabilitation Services and (5) Research Division. At the same time, the New Westminster Mental Hospital was re-named Woodlands School in keeping with its function, although

direct admission would not take place until 1953; the word "attendant" was deleted from the Civil Service structure; and the Provincial Mental Hospital's "Chronic Buildings" were re-named "Lawn Buildings", thus up-dating the semantics of mental illness. Pennington Hall, containing a café, bowling alley and theatre, was opened, as were increased facilities for the aged at Terrace and for the patients at Woodlands School. The Nursing School at this time had centralized its training, heretofore carried out independently by both mental hospitals, and commenced a "block system" for its 230 female and 190 male students. In addition, the annual report for this year, 1950, carried the nomenclature of the American Psychiatric Association, thus spelling an end to the system that had been used for many decades.

In 1950, the Medical Faculty of the University of British Columbia started to train its first class of undergraduates. High hopes were expressed in the annual report for the year that the new school would be of great assistance with the vexing problem of postgraduate training for resident physicians of the mental health services, who were, by this time, severely restricted by regulations formulated by the Royal College of Physicians and Surgeons. They could, for example, receive credit for only one year towards certification, regardless of the number of years spent in the Mental Hospital, and further, were to be encouraged to train in several centres rather than remain in the same geographical area. By 1961, a firmly organized, integrated scheme was yet to be developed, although co-operation in many fields, particularly neurological research, had continued.

On January 1, 1951, "The Clinics of Psychological Medicine Act" was proclaimed and ". . . for the first time it became possible to receive patients at an earlier stage of their illness." This moment, long sought, caused plans for a second large hospital to be shelved and stimulated thought on the next advance—the reaching further into the community with day hospitals and outpatient clinics. This latest Act made voluntary admissions and certified admissions without loss of civil rights possible for a maximum period of four months.

The first year of operation of the Crease Clinic was indicative of success: 791 of the 963 patients admitted were returned to the community within the statutory period. During this year (1951-1952), the first consultants in general surgery and neurosurgery were retained by means of a "Mental Health Grant" and a survey of overcrowding was made at the request of the Federal Government. The results of the latter were shocking! One building (the male side of Centre Lawn) was found to be 81.1% overcrowded; that is, a facility designed for 143 patients was housing 260. West Lawn (male), East Lawn (female), and Centre Lawn (female side) were 30.8%, 56.8% and 42.5% overcrowded, respectively.

The year 1951 marked the commencement of a policy to establish "open wards" in the P.M.H. and Crease Clinic. The following year, all forms of physical restraint were, once again, abolished, except for seclusion under strict safeguards. A year later, children under six years of age were permitted direct admission to the Woodlands School, thereby ending the tragic mixing of small patients with adults suffering from various types and degrees of mental disorder.

During 1951, a research "colony" was established at the University under Dr. W. Gibson, and investigations were begun. 1952 saw the opening of operating-room facilities in the Crease Clinic. Since the peak days at the Public Hospital for the Insane, all surgical operations, at great inconvenience to all, had to be carried out either at the Royal Columbian Hospital in New Westminster or the Vancouver General Hospital. This year, a re-motivation program for the long-neglected patients in the "chronic" buildings was started in the female building, and in harmony with this increased activity, regular ward rounds were commenced and two social workers were appointed to begin full-time work on two wards in the Provincial Mental Hospital. Alcoholics, long refused admission for treatment, were allocated 25 beds in the Centre Lawn building.

In 1953, a "School for Mental Defectives Act" became operative on October 1. Woodlands School at this time had 1098 patients "on the books" and a growing waiting list. On the wards of both the P.M.H. and the Crease Clinic, the "relationship" or "milieu" therapy was incorporated into the teaching program, and the team approach of physician, nurse, psychologist and social worker was stressed. Insulin coma therapy, which had been discontinued at the P.M.H., was re-introduced and marked the point at which treatments available in the Clinic were also in use in the P.M.H. Group psychotherapy, including a program for an adolescent group, was practised; volunteer workers organized by the Canadian Mental Health Association (C.M.H.A.) appeared for the first time on the wards, and outpatient services were established for discharged patients, to be used especially by those residing in the nearby geographic area.

On April 1, 1954, the Neurological Research Centre that had published an impressive list of titles and whose members had presented papers to numerous societies, was formally transferred to the University to become the Department of Neurological Research.

By March 31, 1955, there were five unlocked wards in the P.M.H. and the Crease Clinic, serving 537 patients. Definite progress was being made. General paresis, the scourge of so many years, was practically eliminated. Epilepsy was under control, and it was calculated that at least 50% of schizophrenics could be assisted back to the community after a relatively short period of treatment. Chlorpromazine and reserpine were added to the armamentarium of therapeutic agents.

By this time too, the community's involvement in the treatment of mental illness was obvious and it had such representatives as the C.M.H.A. volunteers, and the Auxiliary formed at Woodlands School by the B.C. Society for Handicapped Children. The personnel of the Provincial Mental Health Services participated in many of the community-sponsored efforts in the field. They assisted in the Mental Health Training Program that was held under the direction of the Vancouver School Board, in addition to advising the Alcoholism Foundation of B.C., and the Narcotic Addiction Foundation.

On May 4, 1955, a centre for the treatment of tuberculosis, the North Lawn building, containing 230 beds, was opened after many years of anticipation.

On January 2, 1957, the Mental Health Centre in nearby Burnaby was opened. This unit provided accommodation for the Child Guidance Clinic which was freed from its long residence in antiquated, inadequate quarters, and was to provide outpatient services and a day care centre for the community. The same year, the quarters vacated by the Child Guidance Clinic were converted into "Venture", a rehabilitation centre for men.

Dr. Gee retired on August 31, 1958, and his position as Director was taken by Dr. A. E. Davidson. The next year the Mental Health Services were removed from the Provincial Secretary's Department where they had been since 1872 and were transferred to the Department of Health Services and Hospital Insurance. Dr. Davidson became a Deputy Minister representing the P.M.H.S. and moved his offices from Essondale to Vancouver.

During the 1959-1960 fiscal year, considerable expansion took place in the areas dealing with the aged and the mentally defective: an infirmary building named the Valleyview Building was opened at the Homes for the Aged, Port Coquitlam, and 130 males were transported from Woodlands School to Tranquille, a recently vacated sanitorium at Kamloops, no longer required for the treatment of large numbers of tuberculosis cases. At Essondale, approximately 70% of the patients were living on open wards and the results of 10 years of increased therapy were now available for comparison and were cause for exultation. In 1948-1949, the total population increased by 354 with an index increase of 28.09. In 1959-1960, the increase was 20 with an index of 0.61%. The total admissions in 1948-1949 were 1260; in 1959-1960, 3294. For the first time in history, there were actual decreases in the resident population; 78 patients fewer in 1956-1957, and 90 fewer in 1958-1959.

SUMMARY

The history of the treatment of mental illness in the Province of British Columbia is, in large degree, the history of the development of the Provincial Mental Health Services. This extends now from 1872 to 1961. Starting as an institution to provide custodial care chiefly for the dependent insane, it developed prior to the First World War into a model demonstrating the principles of the "moral treatment" of mental illness that were in vogue in that day. This was followed by a long interval, marked at each end by a devastating war and plagued throughout by episodes of economic depression. During this time there was a slowing down of construction and a consequent building up of an overcrowding problem in addition to a periodic shortage of trained personnel that not only reduced the efficiency of the organization as a treatment centre but re-introduced some, at least, of the restraining practices of a previous barbaric time. During this period, however, sporadic but important advances were made that were available for development during the resurgent period of the last decade.

During the resurgent period, there have been some definite advances as shown by statistics (and when scrutinizing these we must keep in mind the sobering facts that there is a long waiting list for Woodlands School and for the Homes for the Aged and that many of the persons discharged from the long-term buildings in the P.M.H. remain public charges in boarding and nursing homes). There has, in addition, been a re-establishment of the "hospital" amosphere with wards made as cheerful as is consistent with continued overcrowding. Facilities for occupational therapy, recreation, and amusement have been improved, as have the means for providing treatment — psychiatric, medical, and surgical — to those patients to whom these can bring benefit. Finally, there are encouraging signs of rising community interest in mental illness and commencing expansion of the mental health services to provide facilities within the community itself to all who can be accommodated with no regard for socioeconomic status.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

PRIMARY TUMOURS OF THE BLADDER

It must be remembered that new growths of the bladder are not so uncommon as one would be led to suppose from the teaching of the past. Out of 1667 cases of new growths in the Royal Victoria Hospital in the last fifteen years, there were 30 which occurred in the bladder. A. von Frisch, of Vienna, collected 300 cases from his clinic in twenty years, and Nitze, after the introduction of the operating cystoscope, had 150 cases. The statistics of Kuster from the Augusta Hospital showed 0.25 per cent. of bladder tumours out of 19,267 cases of new growths, and Gurlt found 0.39 per cent. out of 1663 tumour cases.

As to the cause of tumours of the bladder, we are as much at sea as we are in the case of tumour formation in general. We can only speak of certain things predisposing to the formation of new growths, and these are essentially irritants. They comprise the chemical, mechanical, and bacterial. How prominent a part these play in their formation is a disputed point at the present day.—William Hutchison (Montreal), *Canad. M. A. J.*, 1: 872, 1911.

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SHORT COMMUNICATION

BELATED DIAGNOSIS OF STEATORRHEA

RALPH SPITZER, Ph.D., M.D.* and
J. A. RYAN, M.D.,† *New Westminster, B.C.*

ALTHOUGH it is recognized[1] that steatorrhea may present with a wide variety of symptoms, the diagnosis is often missed, even in the presence of one of the classical modes of its presentation. The young man described in this report had suffered from undiagnosed hypochromic anemia for many years, after which he had episodes of severe intermittent hemarthroses, but was not investigated for steatorrhea until he was admitted to hospital with overt tetany.

In addition to the interesting clinical features of this case, this report demonstrates that reasonably adequate investigation of this condition can be carried out in a medium-sized hospital and in as short a period of time as seven days.

METHODS

The Royal Columbian Hospital, New Westminster, B.C., does not have a metabolic ward or research unit, and investigation requiring uncommon procedures must be carried out with the least possible additional burden on our routine laboratory. Some of the improvisations used during this study may be of interest to other general hospitals without special research facilities. The methods employed will be described in more than the usual detail.

Serum calcium and magnesium are determined by manual EDTA titration of whole serum using "Cal-Red" as indicator for calcium and Eriochrome Black T for the sum of calcium and magnesium.[2] The endpoint is determined visually and, as long as the lighting is adequate, there is no difficulty in duplicating results to 0.1-0.2 mEq./l. Both determinations can be done in three or four minutes.

In the xylose tolerance test, 25 g. of d-xylose are given orally after collecting a fasting specimen of urine. The total reducing substances are determined by the Auto-Analyser on a five-hour specimen of urine. Correction is made by assuming that the non-xylose reducing substances have the same concentration in the test specimen as in the fasting specimen. A recent paper[3] describes a similar method for doing xylose tolerances, and shows that this assumption is valid.

Total stool fat, on a ward diet which includes at least 70 g. fat per day, is determined by collecting a 48-hour specimen, diluting it to a standard volume, homogenizing, and analyzing an aliquot by a modification of the method of Van deKamer.[4] Daily excretion of more than 6 g. of fat is considered to be evidence of steatorrhea.

Total serum cholesterol is determined by the method of Carr and Drekter,[5] a simple procedure which has been shown[6] to give results equal to the Schonheimer-Sperry method in reproducibility. Determination of the serum carotene[7] requires only a single extraction of serum with petroleum ether and a reading taken at 440 mμ. Values below 70 μg./100 ml. should raise the suspicion of steatorrhea. Screening for coagulation defects is done by the one-step Quick prothrombin time and the partial thromboplastin time (P.T.T.).[8] Known defective plasmas are used to correct the P.T.T.

The remaining laboratory work is done by standard methods.

CASE REPORT

O.H., a 31-year-old mill worker, was admitted to hospital because of severe muscle spasm. For about six weeks he had noticed "tightening" of the muscles of his upper extremities and chest. He had difficulty using his fingers and was sometimes short of breath. It was hard for him to speak distinctly, but he did not have difficulty in finding the necessary words. He had had one similar, although milder, episode six months earlier. For many years he had suffered from mild anemia which, though not investigated, had responded to oral iron. In 1957 the patient was admitted with severe multiple hemarthroses of his left lower extremity. The bleeding was found to be caused by PTC and factor VII deficiency. He was treated with whole blood, plasma and vitamin K. His coagulation defect varied from time to time, as shown in Table I. Although he has never had any serious illnesses, he has never felt really well. His appetite had always been very good, but his weight remained subnormal. On further and repeated questioning he admitted to intermittent diarrhea since his early teens, with episodes lasting as long as four months with 3-4 stools daily. His father died of carcinoma of the lung at the age of 43. His mother and one brother are alive and well. Two sisters, one of whom is undergoing treatment for myxedema, have been treated for anemia; the other has suffered from chronic diarrhea since the birth of her last child. Her brother, the present patient, suggested a gluten-free diet to her which controlled her symptoms.

TABLE I.

Date	*Prothrombin time*	*Partial thromboplastin*
October 1958	45%	95 seconds
November 1958	78%	100 "
February 1959	65%	82 "
April 1959	20%	138 "
May 1959	95%	62 "
June 1959	26%	78 "
February 1960	11.5%	66 "
May 1960	21%	95 "
November 1960	70%	83 "

*Director, Biochemistry Laboratories, Royal Columbian Hospital, New Westminster, B.C.
†Resident in Pathology, Royal Columbian Hospital.

The only positive findings on physical examination were absence of knee and ankle jerks and positive Chvostek's and Trousseau's signs. The patient's height was 5 ft. 8 in., and his weight 143 lb.

Investigation.—On admission his serum calcium and magnesium were 2.3 and 0.75 mEq./l. respectively, and his hemoglobin was 11.4 g./100 ml. The serum carotene was 2.5 μg./100 ml., cholesterol 115 mg./100 ml. and phosphorus 3.6 mg./100 ml. He excreted 2.2 mEq. (44 mg.) of Ca, 2.3 mEq. of Mg., and 1.9 g. of phosphorus in his urine in 24 hours; 0.9 g. xylose in 5 hours and 59 g. fat were excreted per 24 hours in the stool. The blood glucose levels during a glucose tolerance test were 75, 81, 86, 83 and 82 mg./100 ml. His prothrombin time was 18 seconds (control 12.5 seconds), and P.T.T. 127 seconds (control 75 seconds).

Serum sodium, potassium, chloride, bicarbonate and serum protein determinations were normal. His anemia was hypochromic, with no evidence of macrocytosis.

Radiologic examination showed "distended loops and segmentation, consistent with idiopathic steatorrhea (or pancreatogenous steatorrhea), lymphoma of the small bowel, or Whipple's disease". Skeletal radiographs showed evidence of general demineralization with osteomalacia.

During his hospital stay he was treated with intravenous and oral calcium and dihydrotachysterol (Calciferol). His serum calcium rose to 3.1 mEq./l., and all symptoms subsided. He was discharged on the 8th day on a gluten-free diet, and replacement with calcium lactate tablets 3 g. q.i.d., and dihydrotachysterol 50,000 units per day.

Follow-Up.—After six weeks of this regimen his serum calcium was 4.5 mEq./l., prothrombin time 16.5 seconds and serum carotene 57 μg./100 ml. His diarrhea was much better, and he felt that he was in better health than he had ever enjoyed previously. All medication was discontinued except his gluten-free diet. A second follow-up examination four weeks later showed a serum calcium of 4.3 mEq./l., carotene of 70 μg./100 ml., cholesterol of 110 mg./100 ml., prothrombin time of 14.5 seconds and a hemoglobin of 82% (12.1 g. %). He excreted 4.4 g. of d-xylose in five hours. The patient continued to feel well and now weighed 167 lb. The pertinent findings are summarized in Table II.

TABLE II.—BRIEF SUMMARY OF PATIENT'S PROGRESS

	On admission	*6 weeks*	*10 weeks*
Weight (lb.)	143	157	168
Serum carotene (μg./100 ml.)	2.5	57	70
Hb. (g./100 ml.)	11.4 (76%)		12.1 (82%)
Serum calcium (mEq./l.)	2.3	4.5	4.3
Prothrombin time (seconds) (control 13 seconds)	18	16.5	14.5
5-hour xylose excretion (g.)	0.9		4.4

DISCUSSION

This patient probably had a long-standing anemia due to defective intestinal absorption and, perhaps, aggravated by bleeding into the joints. No history of diarrhea was obtained until repeated questioning on his last admission elicited that this symptom had been present for some time.

In spite of laboratory evidence of almost complete lack of absorption of fat and carbohydrate, this patient's serum proteins were normal and his weight was almost normal, probably because of his excessive appetite. He had been able to carry on at his work in a lumber mill up to the time of admission.

This case provides a good demonstration of the puzzling variability in absorption defects shown by sufferers from steatorrhea. Along with this patient's very poor fat absorption there was malabsorption of calcium, magnesium, and probably vitamin D, but the defect in vitamin K absorption appeared to be sporadic. Proteins would seem to be absorbed well, and there is no evidence in the hematological examination of any defect of hematopoietic factors except iron.

Our simplified scheme for investigation of steatorrhea lays heavy stress on the serum carotene determination as a screening test. It has been shown[7, 9] that only a small number of patients with steatorrhea, and those usually the mildest cases, will have a carotene level above 70-80 mg./100 ml. This test is so easy to do that it is recommended as a screening test in all patients with obscure anemia, coagulation defects, weight loss, or any of the other possible presenting symptoms of steatorrhea. That other causes, such as simple malnutrition or liver disease, can lead to a low carotene level, does not mitigate against the determination as a screening test, because the presence of a low carotene level demands a stool fat analysis to complete the differential diagnosis.

SUMMARY

A patient with gluten-induced steatorrhea is presented who was considered for many years to have anemia due to undetected blood loss.

A simple and rapid method of investigation, within the resources of any medium-sized hospital, is proposed.

The nature of the defects of absorption in this patient has been determined approximately by the investigation.

We wish to thank Dr. John A. Graham for making this patient available for study and Dr. D. G. Murray for investigating the coagulation defects. Miss W. Bouma and Mr. C. Pilbeam gave invaluable assistance in performing the laboratory work.

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THE SAFETY OF BLOOD TRANSFUSIONS

AN article, "Three Blood Transfusions out of Four Are More Likely to Harm Than to Heal" by Dr. F. B. Bowman and Sidney Katz, which appeared in *Maclean's* magazine on August 26, 1961, prompts us to feel concern as to the role of the lay press in the publication of an article of this nature, as well as to its scientific merits. In our opinion, this article gives a distorted picture and is a superficial and misleading treatment of a highly complex subject, amounting to a gross misrepresentation of the role and value of blood transfusion. Even with the implied apology in its final paragraph: "Despite the hazards involved, blood transfusion remains a unique medical tool and should not be abandoned . . . etc.", this article may further jeopardize the slender supply of blood available for transfusion purposes.

The periodical responsible for this unfortunate piece has its editorial offices within a few blocks of several major hospitals of international repute, the University of Toronto and its medical school, and the National Reference Laboratory of the Blood Transfusion Service of the Canadian Red Cross. The most detailed and authoritative advice on the many facets of this complex matter was readily available but was passed over. The co-author of this extraordinary article, a veteran doctor, may well have completed much of his active professional career before the main body of knowledge which makes up the specialty of immunohematology became available; the Rh factors were not described until 1940 and clinical laboratory tests for the presence of these factors were not applied until after 1946.

In any case, if Dr. Bowman has a serious communication to direct to his fellow physicians, particularly when his message is one of far-reaching criticism of methods of practice, the Code of Ethics* indicates how this is to be done. Furthermore, "All opinions on medical subjects which are communicated to the laity by any medium, whether it be a public meeting, the lay press, radio or television, should be presented as from some organized and recognized medical society or association and not from an individual physician. Such opinions should represent what is the generally accepted opinion of the medical profession."†

In recent years this Journal has published many scientific papers by recognized experts in this field, such as Chown,[1] Moore[2] and others, that set out in unmistakable terms the risks associated with the transfusion of human blood. Dr. Bowman has contributed 10 communications, chiefly letters to the editor and clinical notes, to the Journal since 1953, but none of them have been devoted to any aspect of hematology or the use of blood transfusions.

The process of transmitting the most recent knowledge on the proper use of this unique and highly complex substance has been, and continues to be, carried on by medical schools, professional journals, and postgraduate assemblies. A particularly important contribution is being made by skilful, devoted physicians working in the laboratories of community hospitals, in university medical centres, in the facilities of the Canadian Red Cross Blood Transfusion Service and the Rh Laboratory in Winnipeg. These professional activities are supplemented by the consultation services and educational programs of certain producers of serological reagents such as the Ortho Pharmaceutical Corporation of Canada Ltd. The experts in this field are men and women with highly specialized training who supervise technicians during the performance of a series of detailed examinations which has given the Canadian people as high a standard of blood transfusion service as is available anywhere in the world.

The records of three Canadian hospitals illustrate this achievement:

At the Toronto General Hospital,[3] during the year 1960, 14,696 bottles of blood and 796 bottles of other blood products, fibrinogen, albumin and fresh frozen plasma were administered to 5746 patients; transfusion reactions were reported in 58 (1.09%)—fever 32, urticaria 20, other symptoms 3, "transfusion" hepatitis 3; all of the patients with serum hepatitis recovered. In the previous two years, 1958 and 1959, two patients developed "transfusion hepatitis". One patient each year received an "incompatible" transfusion; the signs and symptoms were recognized and the transfusion was stopped immediately and neither patient developed anuria. The incompatible transfusions were due, in both cases, to clerical error and not to faults in laboratory cross-matching technique. There were

*The Canadian Medical Association Code of Ethics, 1961, p. 11.
†*Ibid.*, p. 10.

no deaths attributed to hepatitis or to the transfusion of incompatible blood.

In Halifax, at the Victoria General Hospital[4] and related institutions, 28,300 blood transfusions have been given in the past five years, 1955-1960. There have been no fatal transfusions and no major reactions due to specific group incompatibility. There were 47 non-specific reactions reported but no episodes of hepatitis due to blood transfusion.

At the Vancouver General Hospital[5] during the period January 1948 to August 1961, 133,623 blood transfusions were given and 1397 reactions of all types were reported, a rate of 1.04%. In the period 1958 to 1961, 414 patients had 492 reactions: hemolytic 3, allergic 191, pyrogenic (fever) 265, cardiac overload 2 and indefinite 31. Each year two or three patients have pyrogenic reactions of considerable severity; the majority of these patients are suffering from complex blood diseases or other illnesses which require transfusion over a prolonged period. There were three hemolytic reactions; two were not serious but in the third, a patient with multiple antibodies, the reaction may have contributed to his death. In the past four years, there have been 25 cases of probable "transfusion" (homologous serum) hepatitis; in one, death was probably directly due to the hepatitis and in two others this complication was a contributing factor; all the other 22 recovered uneventfully. Almost all the patients in this group who developed hepatitis had serious underlying disease and received many bottles of blood as treatment. Approximately 45,000 transfusions were given during the period in which the 25 cases of hepatitis occurred, a rate of 0.055%.

Human blood is a highly complex substance; many of its components are protein in nature and have antigenic potentials, both inherent and acquired. Hematology, and its companion study immunohematology, have undergone a dramatic expansion in the years since the end of World War II. A variety of reactions which contributed to the risk of blood transfusion before that time have been prevented by improvements in blood typing; for example, most of the tragedies, cited by Chown[1] and others, in which girls and young women received antibodies during a transfusion which later resulted in miscarriage or intrauterine fetal death, occurred before Rh typing of blood donors became routine practice. Furthermore, in over 14 years' experience with the Canadian Red Cross Blood Transfusion Service, involving the transfusion of over 3,000,000 bottles of whole blood, no instance of transmission of disease by means of transfusion has been encountered other than the relatively small incidence of infectious hepatitis. This was related almost entirely to the use of dried plasma; this material has been replaced entirely by the more effective and safer blood protein fraction, plasma albumin.

Before newer knowledge about the less common blood group incompatibilities and the transmission of the virus of infectious hepatitis became available, the transfusion of blood was looked upon as a relatively harmless, supportive measure, but this attitude has largely disappeared in the last decade.

The responsibility for cross-matching blood for individual patients has been returned to the hospital laboratory in every province except Alberta, Manitoba, Nova Scotia, Prince Edward Island and parts of Saskatchewan. In these areas, it is still carried on by the Canadian Red Cross Blood Transfusion Service. All supplies of blood are obtained from volunteer donors, recruited by the Canadian Red Cross Society throughout Canada. The blood is collected by the Society's Blood Transfusion Service and grouped, typed and tested serologically for syphilis in its laboratories before it is distributed to hospitals on requisition. A high standard of screening to detect a wide variety of potentially incompatible factors is in force and immediate consultation is available in difficult cases with the regional medical director of the Canadian Red Cross Blood Transfusion Service and through him with the medical director of its National Reference Laboratory in Toronto. These safeguards have reduced technical errors in the choice of blood for transfusion to a minimum. Hemolytic reactions still occur infrequently but are due, in over 60% of cases,[2] to human errors elsewhere in the chain of events between the taking of a specimen of blood for cross-matching and the eventual infusion of it.

The article "Three Blood Transfusions out of Four Are More Likely to Harm Than to Heal" does not prove, or come near proving, the sensational charges contained in its title and sub-title. It alleges that 75% of blood transfusions given in Canada are either unnecessary or do positive harm, yet Dr. Bowman gives no statistics dealing with the Canadian experience on which these charges could be assessed.

The lay reader is not informed in this article that the transfusion of blood is not a definitive form of treatment complete in itself. Blood transfusion is an adjunct to therapy, a supporting step in a complex pattern of medical or surgical measures.

The use of any treatment involves a balancing of risks in which the benefit to be achieved is measured against the risks inherent in the procedure; it is an exercise of professional judgment for which only the physician is prepared. The necessity of blood transfusion can be judged only when the *specific* patient's problem is examined in the light of sound clinical knowledge. Dr. Bowman has lumped together 375,000 of these complex situations and has issued a sweeping condemnation.

The difference between the Bowman-Katz article and a scientific examination of one segment of this complex problem can be seen when it is compared with a paper such as Graham-Stewart's,[6] "A Clinical Survey of Blood Transfusion". This investigation

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of the use of 1112 bottles of blood or blood substitutes was carried out in a London hospital in a four-month period in 1960. To determine whether or not a transfusion was *clinically justified*, the following criteria were used:

"1. Single-pint transfusions should not be given to adults.

2. Where anemia is not due to acute blood loss, it should be treated by transfusion only if it will not respond to drugs.

3. Patients dying of incurable disease should receive blood only if anemia is the cause of their symptoms, and if its correction will be followed by a period of enjoyable existence.

4. Preoperative transfusion is indicated by the urgency and not the expediency of the operation.

5. Massive acute blood loss requires rapid and adequate replacement of red cells and plasma.

6. Moderate acute blood loss does not require transfusion of red cells (as opposed to dextran or plasma) unless it is causing, or is likely to cause, significant anemia.

7. Positive postoperative transfusion is indicated more by the extent of residual pathology than by the presence of anemia."

On the basis of these criteria, 64 bottles of blood were found to have been given unnecessarily, amounting to 6.5% of the blood used: as single pints, 16; for "medical" anemia, 3; for dying patients, 4; in the inadequate preparation for surgery, 11; in moderate acute operative loss, 6; in the expectation of further loss, 18; for the treatment of postoperative anemia, 2; and for postoperative collapse, 4.

This result, from a leading teaching hospital, is probably better in degree than that achieved in smaller hospitals but it is not likely to differ in kind.

It should be noted especially that this assessment is the result of the application of rigid criteria *after the event;* the decision to use blood transfusion or any other medical measure can be made only by the physician in charge. For example, in this series 18 transfusions were given in "expectation of further [blood] loss". This is a familiar situation; the patient is in good general condition but has lost an unknown but significant quantity of blood into the bowel. The need for the replacement of blood depends largely on the answer to a single question, "Will he continue to bleed?". If the patient continues to bleed, his state becomes increasingly dangerous from hour to hour. The physician's response depends on many variables such as: the availability of blood; the availability and convenience of facilities and personnel to carry out surgery to control the bleeding; and the patient's general medical condition. Whatever decision is made, it will not be the same in every instance, for the best rules are but guides; what is right, necessary and life-saving for Mr. Jones in a remote town, at 2 a.m. Sunday morning, may seem unnecessary for Mrs. Smith in a large hospital on a week day.

Dr. Bowman's condemnation has an additional misleading aspect. It ignores the many surgical and medical procedures of recent origin that depend entirely on the availability of large amounts of blood, the surgical treatment of lesions of the heart and great vessels such as the correction of congenital heart lesions and repair of aneurysms of the aorta, major operations on the gastrointestinal tract, and the palliation and occasional cure of the various forms of malignancy. The transfusion of blood in the leukemias and lymphomas does not "heal" but it is an essential part of an increasingly effective branch of medical treatment which provides a significant period of enjoyable existence for these unfortunate persons.

The probable harmful effects of the Bowman-Katz indictment can be neutralized gradually by the practising physician and the hospital administrators who are dealing with individuals and families strongly motivated to accept professional advice and service. If, when blood transfusion is recommended as part of the treatment, the patient or the family demurs, the doctor can explain in more detail the necessity for this measure and can suggest that the opinion of a second physician be obtained. These and similar potential misunderstandings can be discussed with the patient or his relatives as they arise. However, the Canadian Red Cross, a voluntary humanitarian organization whose services have been of untold benefit to the Canadian people, has no such opportunity to explain its position to the individual Canadian. A unique medical institution, the Canadian Red Cross Blood Transfusion Service, which has been brought through years of patient labour to a high level of technical perfection, has been impugned in an article in a national magazine in which three-quarters of its activities have been called either useless or harmful.

Articles which lack a balanced appraisal can do widespread damage to an important facet of modern medical practice, although the good sense of some readers will prevent them from needless alarm. The proprietors of the newspapers and weekly journals must realize the important responsibility they bear in the transmission of information to the public. Publishing such articles prejudices the process of genuine education. If any responsible person or group desires factual material on medical affairs, the Canadian Medical Association and its Provincial Divisions through the person of the Secretary, or through the county or district medical society, will assist them. The advice of the medical profession is especially necessary in these complex situations on which only a few individuals are competent to speak authoritatively. This approach is recommended in the Code of Cooperation*

*Developed by the Canadian Medical Association with the assistance of representatives of the news media.

which says in part: "On all matters of health and medical news, representatives of the news media should make every reasonable effort to obtain authentic information from qualified sources before proceeding to publish or broadcast. The news media should make every effort to seek out spokesmen designated by the local medical society . . . " The Canadian Medical Association wishes the public to have the best scientific information available and the opinion of a single physician is no substitute for this. It is not the desire of the Canadian Medical Association, or any of its officers, to control or censor what is finally written, but to ask that the material be obtained from representative sources.

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CONTROLLED DRUGS

AT THE latest session of Parliament, the Food and Drugs Act was amended to provide for more effective control of amphetamine and its salts, barbituric acid and its salts and derivatives and methamphetamine and its salts. These drugs, which were frequently referred to as "goof balls" during the debates in the House of Commons, are now officially known as Controlled Drugs. The degree of control of these drugs is only less stringent than that applied to narcotic drugs, and physicians must accommodate themselves to the new situation.

Part G of the Food and Drug Regulations, effective September 15, 1961, has just been issued. It provides for the licensing of importers and dealers in Controlled Drugs and for the recording of all transactions involved in their distribution.

Pharmacists may procure Controlled Drugs only from a licensed dealer and may dispense them only on the signed and dated prescription of a practitioner or, under exceptional circumstances, on the verbal order of a practitioner known to the dispenser. The same principles apply to controlled drugs obtained by doctors for use in their practices.

It is worthy of note by every doctor that "A pharmacist shall not refill a prescription for a controlled drug unless the practitioner, at the time the prescription was issued, has so directed in writing and specified the number of times and the dates that the same may be refilled; and the pharmacists shall keep a record of each refilling of a prescription."

The following regulations, slightly modified to eliminate the references to veterinary medicine, specify the obligations of physicians in the current situation:

"G.04.001. No practitioner shall prescribe, administer, give, sell or furnish a controlled drug to any person unless

(a) the person is a patient under his professional treatment; and

(b) the controlled drug is required for the condition for which the patient is receiving treatment.

"G.04.002. A practitioner shall, on request, furnish to the Minister such information as the Minister may require respecting controlled drugs purchased by the practitioner or the prescribing, administering, giving, selling or furnishing of a controlled drug by the practitioner to any person and the practitioner shall keep such books and records respecting controlled drugs purchased, prescribed, administered, given, sold or furnished as the Minister may require.

"G.04.003. Where a practitioner alleges or, in any prosecution for an offence under the Act or this Part, pleads that his possession of a controlled drug was for use in his practice or that he prescribed, administered, gave, sold or furnished a controlled drug to any person as a patient under his professional treatment and that such controlled drug was required for the condition for which the patient received treatment, the burden of proof therof shall be on such practitioner.

"G.04.004. Where, in the opinion of the Minister, it is necessary to do so for the proper administration and enforcement of the Act or this Part, the Minister may refer to the appropriate provincial licensing authority of any province in which a practitioner is registered and entitled to practise information obtained under this Part, together with any other information he considers relevant, and following consultation with such provincial licensing authority, may, notwithstanding anything contained in this Part, impose such conditions as in his opinion may be desirable in the public interest on the right of such practitioner to purchase a controlled drug."

It will be observed that the legislation and regulations are designed to preserve the use of Controlled Drugs for legitimate treatment needs and to eliminate the illicit trafficking which has become a problem in certain areas. This purpose will command the support of physicians. They are urged to co-operate in all respects with the pharmacist in providing the necessary prescriptions and in advising patients of the new requirements.

A.D.K.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Some valuable and suggestive results have recently been obtained by researchers into the statistics of the Winnipeg and Toronto General Hospitals. In the latter, Dr. Ryerson finds that an analysis of the records since 1905 shows that gall-stones are more frequently found between the ages of fifteen and forty-five than in persons over forty-five years, the period when, according to the text-books, they are supposed to be most common. This suggests, as Dr. Ryerson points out, the possibility of a much earlier diagnosis and the value of a speedy operation.—*Canad. M. A. J.*, 1: 890, 1911.

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Letters to the Journal

ACRIDINE ORANGE FLUORESCENCE IN CYTOLOGY

To the Editor:

Reference is made to the recent article by Drs. C. F. A. Culling and P. S. Vassar, entitled "Acridine Orange Fluorescence in Cytology of the Cervix" (*Canad. M. A. J.*, 85: 142, 1961), reporting the results of application of the acridine orange (AO) fluorescence method to exfoliative material from 500 gynecological cases; the AO method proved apparently inferior to the (control) Papanicolaou method. It seems pretty obvious, however, that unsuitable application of the fluorescence method was responsible for the unsatisfactory results. The reason may have been a misunderstanding of its cytochemical basis that may have arisen from some rather misleading previous reports.

The AO method demonstrates, by an orange or red cytoplasmic fluorescence, cells that are rich in ribonucleic acid (RNA). RNA is abundant in some secretory cells (e.g. endocervical), and in cells that actively proliferate. Among these are normal basal cells that divide for cell renewal, and endometrial cells that reconstruct the endometrial glands and surface epithelium once about every 28 days; likewise rapidly proliferating malignant cells contain ample RNA. Such cells, normal and abnormal, appear with the AO method in shades of red and orange; most other cells, with no or little RNA, fluoresce greenish or brownish. Red fluorescence thus cannot be specific for cancer cells only, because any normal cell rich in RNA likewise shows reddish fluorescence. No claim of such specificity has ever been made in the original accounts of the AO method (e.g. L. von Bertalanffy *et al.*: *Cancer*, 11: 873, 1958), in which both morphological and cytochemical features of normal and malignant cells, as they appear with the fluorescence method, have been described. Malignant cells are similar cytochemically, in various respects, to undifferentiated normal cells such as basal cells (*Acta cytol.*, 5: No. 4, 1961), and this is apparent also with the AO method. Nevertheless, some workers have attempted to base final diagnoses of cancer on the observation of increased cytoplasmic fluorescence only, disregarding the morphological features of these cells. An example of such investigations follows.

I should like to comment briefly on the three publications to which Drs. Culling and Vassar have referred to support their findings. One by Kornfield and Werder (*Cancer*, 13: 458, 1960) describes the application of the AO method to cells grown in tissue culture. They observed that non-malignant cells which rapidly proliferate in tissue culture (and thus obviously contain large amounts of cytoplasmic RNA) also showed red fluorescence. They then stated that AO was not a "cancer stain" and that red fluorescence was not specific for malignant cells. These statements were, of course, quite unnecessary because such claims of specificity have never been made by the originators of the AO method. I have been informed by letter from Dr. Kornfield that these authors have never applied the AO method to exfoliative material.

The second publication by Umiker *et al.* (*Brit. J. Cancer*, 13: 398, 1959) described an investigation in which three AO stained smears (mostly of respiratory material upon which evaluation is often more difficult) were rapidly scanned within less than four minutes (i.e. only little more than one minute per smear); the interpretations were compared with those obtained on the same smears restained by Papanicolaou's method, and carefully worked out for eight minutes per smear. Also in this investigation the AO interpretations were based on cytoplasmic fluorescence only. It is remarkable that the overall sensitivity of the AO method was as high as 83%. Were the two procedures reversed, it is doubtful that a similar high sensitivity would be achieved by the conventional method.

The third publication, by Liu (*A.M.A. Arch. Path.*, 71: 286, 1961), described an alleged failure of the AO method when applied to 1200 gynecological cases. Unfortunately, in this investigation the technique had been altered to such an extent as to result in almost complete loss of specificity of AO for nucleic acids and thus also of morphological detail. A different, pH 4, citric acid buffer was used that has never been recommended with the original fluorescence method; this was combined with differentiation in calcium chloride (with a pH close to 7). This and other factors rendered this technique unsuitable for cytodiagnosis. It is remarkable that even with this inferior technique only one malignant case was actually missed.

In the investigation by Drs. Culling and Vassar, the final diagnoses of cancer were likewise based on cytoplasmic fluorescence only, without regard to morphological features of the cells showing increased fluorescence. The latter procedure is imperative for the reasons indicated above. This is evident from the large number of false positive interpretations (2%) and the excessive number of suspicious cases (about 10%). Similar results are obtained in prescreening, whereby those smears are singled out that contain cells showing increased fluorescence (Connally and Wall: *Texas State J. M.*, 56: 846, 1960); such a procedure does not, however, yield final diagnoses of cancer.

Because the exact nature of the material has not been stated, the exact reason for the large number of false AO negative diagnoses (almost 2%) cannot be explained. This may occur particularly in studies of exfoliated material from patients undergoing radiotherapy, if one were to rely solely on the orange-red warning signal present in routine material. Particularly during the later stages, only degenerated greenish fluorescent tumour cells may be present. Thus for evaluation of irradiated material, the AO method must be applied largely on a morphological basis.

For comparison I may mention that in our fluorescence series, including all types of routine exfoliative material, one false AO negative interpretation occurred in about every 800 cases; the majority of these studies involved material from the respiratory tract. There was no false AO negative diagnosis in our series among 4000 gynecological cases. In another series of 12,508 gynecological cases, screened by the AO fluorescence method at the Second United States Army Medical Laboratory, no false AO negative diagnosis

was encountered; there were six false AO positive interpretations that were also false Papanicolaou positive, however (Col. R. L. Cavenaugh, M.D., personal communication).

These examples—and more could be cited—indicate that there is no appreciable difference in the number of false interpretations that occur whether conventional or AO fluorescence cytodiagnostic methods are used, provided that the latter is applied properly (regarding orange-red fluorescence exhibited by some cells as a warning signal to be further investigated by morphological evaluation of the cells showing increased cytoplasmic fluorescence).

In the course of our investigation (supported by a research grant from the National Cancer Institute of Canada) we have screened the exfoliative material from 8000 cases. These included all types of routine material (gynecological, respiratory, gastric, body effusions, etc.), and that obtained during radiotherapy. The fluorescence interpretations were compared with those obtained independently by hospital and clinic cytologists, using Papanicolaou's method on smears from the identical exfoliated specimens. The results of part of this investigation (on over 4000 cases) have recently been published (*Cancer Res.*, 21: 422, 1961). These studies indicate that the diagnostic reliability of the fluorescence method, when properly applied, equals that of conventional cytodiagnostic techniques. It has also become evident, however, that even though malignant cells, by their striking fluorescence, are more obvious, and the screening process is somewhat faster (about three minutes per smear), the fluorescence method is not a shortcut to oversimplified cytodiagnosis. If one is not content with the advantages it offers and attempts simplifications that demand the impossible, the results will be accordingly inferior; and this is true for any method.

FELIX D. BERTALANFFY, Ph.D.
Department of Anatomy,
University of Manitoba,
Winnipeg, Man.

To the Editor:

With regard to Dr. Bertalanffy's letter we have the following comments to make:

1. We do agree with Dr. Bertalanffy that many people mistakenly believe that acridine orange is a "cancer" stain; indeed this was one of the main reasons for publishing our short paper (*Canad. M. A. J.*, 85: 142, 1961). While agreeing with his comments on the increased concentration of RNA in rapidly growing cells, it remains, as he says, an indicator of activity rather than malignancy and one is left with the morphological details on which to base a diagnosis.

2. With regard to our series of 500 cases, these did not, to our knowledge, contain material from radiotherapy cases.

3. On the question of morphological detail, one cannot but be impressed by the superior image obtained with the Papanicolaou technique as compared with that of acridine orange. We remain impressed with the acridine orange method as a useful histochemical technique for demonstrating RNA (when controlled with RNAse, etc.). Had we been able (as we have tried many times) to devise a mountant which was permanent and of a high refractive index, we believe that it could supplant the Papanicolaou technique because it would combine morphologic detail with RNA concentration.

4. It is probable that, since Dr. Bertalanffy has worked exclusively with this stain from the beginning, his results may have been more accurate than ours. However, this was an objective study of two techniques, and it remains our impression that the acridine orange method is not any faster and not as accurate as the Papanicolaou technique. On the question of time of screening, the cytology laboratory of the British Columbia Cancer Institute is currently screening 800 smears a day from 400 patients (in the original paper it should have read 300 *cases* per day, not smears), and the average time spent on each smear is three minutes. On the basis of accuracy, their established record of 0.13% false negatives and 4% false positives (established by yearly follow-ups on all positive and suspicious smears and 10% of all negatives) would be difficult to surpass.

In summary then, since non-malignant as well as malignant cells give a red fluorescence with acridine orange, these cells must also then be examined for the morphological criteria of malignancy, and this, for reasons already stated, is better achieved using the standard Papanicolaou technique.

Having worked almost exclusively for the past four years in the field of fluorescence microscopy, we should have preferred to recommend the acridine orange technique, but our results have made this impossible. May we, however, pay tribute to the investigations into the field of cytology and fluorescence microscopy made by Dr. Bertalanffy.

CHARLES F. A. CULLING, F.I.M.L.T., F.R.M.S. and
PHILIP S. VASSAR, M.B., B.S.
Department of Pathology,
Faculty of Medicine,
The University of British Columbia,
Vancouver 8, B.C.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

PRIMARY TUMOURS OF THE BLADDER

The treatment of tumours of the bladder is essentially operative, and this may be divided into two classes, namely, radical operations and palliative operations. Naturally the first question which arises is, When should a radical operation be done, and when a palliative one? Everyone who has interested himself in surgery will see at a glance that this is a very difficult question to answer, as the skill and experience of the surgeon will make certain cases operable which to a less skilled operator would be considered inoperable. When one looks at it from the standpoint of the experienced surgeon, all cases in which the growth is confined to the bladder may be said to be operable. Since the development of the operation of double nephrostomy, or ureterostomy, one can remove the whole bladder with a fair hope of obtaining a sufficiently good result to justify such a serious procedure. It is true that the results so far have not been as encouraging as one would have hoped for, but it must be remembered that a large number of the cases so operated on were in very bad condition before operation. We hope that in the future we shall not see such desperate cases as it has been the fate of surgeons to see in the past.—William Hutchinson, *Canad. M. A. J.*, 1: 872, 1911.

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ASSOCIATION NOTES

For the information of their colleagues in other parts of Canada, the College of Physicians and Surgeons of Saskatchewan desires that the text of the July supplementary submission to the Advisory Planning Committee on Medical Care be reproduced. It presents, in summary, the essentials of the proposals of the profession made in January 1961 and, at the request of the Committee, estimates the cost of correcting the observed deficiencies in existing health services as well as the proposals for the extension of medical services insurance to groups of the population not now covered.

THE COLLEGE OF PHYSICIANS AND SURGEONS OF SASKATCHEWAN SUPPLEMENTARY SUBMISSION TO THE ADVISORY PLANNING COMMITTEE ON MEDICAL CARE IN THE PROVINCE OF SASKATCHEWAN*

Mr. Chairman and Members of the Advisory Planning Committee on Medical Care:

We, the representatives of the medical profession in Saskatchewan, welcome this opportunity to make a supplementary presentation to the Advisory Planning Committee.

At your request, we will outline more specifically the proposals which we originally stated to you in January, explaining in some detail the methods of implementation and the costs related thereto. We will, as well, comment on certain presentations made to the Committee which represent the viewpoint of other interested organizations.

We are encouraged by the remarks of your Chairman directed to our representatives at our most recent meeting to the effect that no program of medical services insurance can operate unless it receives the support and the co-operation of the profession.

This conclusion is, we believe, a logical deduction arising from any objective appraisal of programs existing in other countries. The timing of the Chairman's statement, following immediately upon the preparation of reports by the various travelling Sub-Committees, suggests to us that these studies may prove very helpful to the Committee.

The College of Physicians and Surgeons is aware that some of the presentations which you have received did not accept the philosophy which underlies our proposals. A difference in method or approach was advocated by some organizations, whereas others would have us accept arrangements existing in other countries where conditions are entirely different from those found in Saskatchewan.

For example, it is proposed in certain submissions that the remuneration of physicians should be by salary, that group practice be the rule and that the distribution of doctors should be directed. The representatives of the Advisory Planning Committee have seen situations where attempts have been made to institute each of these features and they are aware that conditions in Saskatchewan are quite unsuitable for their application. Lest there be any doubt about the views of the medical profession, we would state again that we firmly believe that fees for services rendered is the only acceptable method of remunerating doctors rendering personal health services where freedom of choice applies. We believe that group practice has certain advantages under appropriate conditions, but that its development cannot be forced and that its application is quite unsuitable for the sparsely settled areas of our province. We believe, further, that our doctors should have the right to select the type and location of their practices. It is our view that good patient care is promoted by the principles which we have stated.

Good patient care and the maintenance and improvement of the quality of care is our primary aim. We are associated with other organized medical bodies in promoting the continuous improvement of medical services by education and by professional self-discipline. These influences together with a continuous supply of well-trained doctors encourage the highest standards of medical practice.

We must recognize that a system of medical services insurance designed primarily to solve the economic problems of health care is not a device which, per se, will guarantee a high quality of service. We must also recognize that the more study one devotes to medical services insurance the less certain one becomes that any single arrangement is ideal for all circumstances.

We are certain that the studies which your Committee has undertaken have made each of you aware of the complexities in the provision of health services and cognizant that medical services insurance is but one aspect of a much larger problem, and that it should not be considered except in the context of the total health services of this province.

These factors were very evident to us in the studies and discussions which resulted in the proposals which the College of Physicians and Surgeons has presented for your consideration. It is because we are aware that no single arrangement for medical services insurance is ideal that we have proposed a program which retains the best components of our present system and supplements these by measures designed to fill the gaps which exist in medical insurance coverage. These methods presume government financial assistance.

It is, as well, because we are aware of the interrelationships which exist between the various component parts of health services, that we must bring to your attention the deficiencies and recommend their correction.

We were very pleased that so many organizations concerned themselves with the documentation of existing deficiencies in health care for the Committee. This augurs well for future co-operation with the government departments concerned.

We have carefully studied these proposals and have, where possible, estimated the capital and continuing costs for those programs which commend themselves to us as priority projects. We recommend acceptance of the following proposals, which when implemented will substantially improve the quality of health service available.

*Presented in Regina on July 9, 1961.

HOSPITALS

Saskatchewan has had a hospital insurance program since 1947. While its operation has been adequate in many fields, we do not believe that its administration has satisfactorily answered a number of acute problems. We, therefore, recommend that the administration be provided with sufficient authority and funds to initiate programs designed to alleviate the shortage of active treatment beds in our larger cities, to provide alternative less expensive accommodation where this is possible, to replace and renew existing obsolete and rundown facilities and to assess the necessity for the continuing existence of some of our smaller hospitals.

We believe that a capital building program of approximately 19 million dollars is required to provide new beds where they are needed and to renovate existing hospitals. This would provide 400 additional beds in both Saskatoon and Regina, and approximately 450 additional beds in the nine smaller cities of the province which are becoming medical centres.

We believe that some saving could be achieved by designing a number of these beds as convalescent beds. Convalescent beds are less expensive both to build and to maintain. Such units attached or adjacent to general hospitals would greatly ease the demand for active treatment beds.

We also believe that a minimum of 950 new chronic care beds should be built, in 50 bed units, near most, if not all, of the 19 hospitals in the province which now have 70 beds or more. This would allow transferral of some patients from active treatment beds and would also provide reasonable access to hospital for older patients when a change in their medical condition requires hospital services not available in nursing homes. The capital cost would be 9.5 million dollars.

A further capital outlay of an undetermined amount is required to subsidize the building of nursing homes which will meet adequate minimum standards and allow the provision of good nursing care. We have noted that in Australia, Government will meet two-thirds of the capital cost of these institutions provided that they are operated by voluntary non-profit organizations.

Inherent in all of these recommendations are increased operating costs as well as new capital costs. We estimate that the increased operating costs would approximate 12 million dollars annually. This would be in addition to the present $35,000,000 yearly operating cost of hospitals. We would hope, however, that some economies could be achieved, particularly with regard to the operation of the small hospitals.

MENTAL HEALTH

For the past few years this Province has been praised for its forward thinking in mental health as exemplified by "the Saskatchewan Plan". Unfortunately, we have been receiving these accolades under false pretenses as this plan has never been implemented.

We believe that the number of patients in the institutions at North Battleford and Weyburn should be drastically reduced. New beds should be made available by building 200-bed units in association with 11 well-located general hospitals. This would allow sharing of physical plants and provide proximity of treatment for physical illness. It would also allow continuity of care in familiar surroundings.

This is an expensive but very necessary program. The capital costs would approximate 22 million dollars. Operating costs would also increase—as well they should. We now spend less than $5 a day for the care of the mentally ill in hospital, whereas we spend up to $20 daily for the hospital care of the physically ill. Raising the standards in mental hospitals to the same standards as the physically sick receive would cost between 15 and 20 million dollars yearly.

The acute problem of our mental health service which relates to the difficulty of attracting and retaining skilled professional personnel will not be entirely corrected by the provision of the physical facilities mentioned. The provision of these facilities and the expenditure of more ample funds will, however, provide a professional climate which will be the basis for greater stability than we have ever enjoyed and will serve to attract the essential personnel.

OTHER PROGRAMS

(a) We believe that a hospital commission should study and implement, if possible, a comprehensive home care program including home nursing, rehabilitation, social welfare services and, if necessary, psychiatric supervision.

(b) Rehabilitation services should be surveyed and augmented. Adequate facilities and personnel for rehabilitation should become an integral part of the proposed convalescent hospital units and the active treatment and chronic hospitals.

(c) Programs should be undertaken for the detection of visual defects and eye diseases in school children and hearing problems in preschool children, including the provision of hearing aids for those who cannot afford to purchase them.

SUMMARY OF COSTS

The specific costs of implementing these recommendations are:

	Capital cost	*Operating cost*
New active treatment and convalescent beds	$19,000,000	$12,000,000
New chronic beds	9,500,000	
Improved mental health program	22,000,000	$15-20,000,000

In addition we have made recommendations relating to nursing home construction, a home care program, rehabilitation, and visual and aural programs, the cost of which cannot be accurately predetermined. We would, however, commend these programs for further study and early implementation.

MEDICAL SERVICES INSURANCE

While the medical profession will consider any recommendations for medical services insurance which this Committee may wish to refer to the College, we believe it to be of the utmost importance that the solutions which you seek or propose should be primarily related to the needs of the people of Saskatchewan. The only broader concept tenable to us is that they should, perhaps, be acceptable to the people of Canada, especially the medical profession, because it is from graduates of our Canadian medical schools that we must find future physicians to provide medical services to Saskatchewan residents.

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The proposals which we have presented to you bear the endorsement of the medical profession of Canada. They are in accord with the Canadian Medical Association's Statement on Medical Services Insurance. They embody the considered opinions of our colleagues across Canada.

In brief, our proposal on medical services insurance may be re-stated:

(a) Self-supporting citizens should be encouraged to insure themselves and their families by subscribing to one of the voluntary programs of medical services insurance.
(b) Three elements of the population require assistance from public funds to permit them to obtain the medical services insurance which they require:
1. Those persons of all ages with low incomes and limited means.
2. Those persons over 65 years of age whose premiums require subsidy in order to bring the premium for their coverage down to that applicable to persons under 65 years of age.
3. Those who are uninsurable at regular rates because of pre-existing medical conditions.

This proposal is realistic. It is suited to the needs of the public. It is less costly to Government than other proposals and is fully endorsed by the profession.

It envisages a means or needs test applied at the local level to determine those in need of assistance. We do not consider that an income determination of this type is a humiliating procedure but rather one which is commonly applied and accepted when persons apply for aid from public funds. We would remind the Committee that any program must include such a test if it envisages a direct payment by families and individuals on a premium or tax basis. In fact, a means test is an integral part of the present hospital insurance program in Saskatchewan.

The cost of such a program varies according to definition. It could conceivably be very high if the criterion "with low incomes and limited means" was interpreted in a manner which allowed the inclusion of a high proportion of Saskatchewan residents. Alternately, the cost would be negligible if too rigid an interpretation were applied.

We have asked officials of local municipalities to estimate the proportion of their residents who would require assistance to meet the cost of medical services insurance premiums. We have concluded that 10% of the population may require such assistance.

This estimate, of course, included persons now covered under Program I and Program II. These persons, for whom care is now provided by the Government and the profession, have been excluded from the following cost projections:

Cost of Reducing Premiums of Persons Aged 65 and Over

To compute this cost we have assumed participation in voluntary programs by 85% of the net (excluding Programs I and II) 65 and over population. Assistance would, therefore, be provided to 54,825 aged persons. Based on payments to the profession at 85% of the current fee schedule, M.S.I.'s current experience indicates a $25 per capita yearly cost for persons under 65 and a $50 per capita yearly cost for persons aged 65 and over. Thus, the cost of reducing costs and premiums for these older persons to the under 65 cost would be 54,825 x $25 = $1,370,625.

We would suggest that the per capita subsidy ($25 or as it may subsequently change) be paid to approved carriers of medical services insurance on the basis of the number of qualified persons over 65 listed on their rolls. This would allow approved carriers to offer coverage to these older persons at the same rates as would apply to other subscribers.

Cost of Subsidizing Premiums of the Low Income Group

We estimate that 10% of the population might reasonably qualify for subsidization of premiums on the basis of low incomes with limited means. Support for this estimate of 10% is provided by the experience of this Province in the financing of hospital care insurance and by the statements of representatives of Health Region No. 1. We recognize, however, that the actual application of a test of financial need might prove that a greater or fewer number of our fellow citizens might qualify for aid from public funds. This estimate, therefore, is a tentative one and we are prepared to accept the result of the application of a means or needs test by the method which we have proposed.

Estimating the population at 918,000 and excluding 33,200 persons covered under Programs I and II, 10% of 884,800 persons or 88,480 would qualify. If the whole of this group needed total assistance it would cost $2,212,000. If we assume that half would qualify for a subsidy equal to two-thirds of the premium, and half qualify for a subsidy equal to one-third of the premium, the total subsidy would amount to $1,106,000.

It is, of course, possible that 20% of the population would require assistance. Assuming that half would require a two-thirds subsidy and half require a one-third subsidy, the total cost of providing assistance would be $2,212,000.

We would suggest that applicants, upon receiving approval of subsidy at a local level, forward their authorization and the amount of premium for which they are personally responsible to an approved carrier. The carrier would then bill the Government for the amount of subsidy involved, using the authorization which they received from the applicant.

The Uninsurables

The remaining group requiring assistance is composed of persons who are by present standards uninsurable at regular rates because of pre-existing medical conditions. It is difficult, if not impossible, to completely segregate these persons on the basis of an application. We would, therefore, recommend that these persons be accepted by approved carriers on the same terms and conditions as other subscribers and that any increased costs arising out of their participation be reflected in the general premium rates applicable to all subscribers.

Summary

The studies of this Advisory Planning Committee have amply demonstrated that any system of medical services insurance should not be developed in isolation from the other health services which are available. It has been pointed out by the College and by many

others testifying before this Committee that existing programs under public and voluntary auspices have fallen short of their optimum development and that the application of additional amounts of public funds will be required immediately to improve these essential health services. Earlier in this submission we have called attention to certain of these deficiencies and have estimated the cost of bringing them up to an acceptable standard. We hope that this Committee will recommend to Government that sufficient moneys be allocated to meet the requirements of these health services.

With regard to medical services insurance, the total cost to Government of the forms of subsidizing premiums, which we advocate, would be $2,476,625 yearly, based on the assumption we have postulated. This amount would change, of course, if a more liberal attitude was taken regarding definition or if costs of providing comprehensive physicians' services altered. (If we assume that 20% of the population would require assistance, the total cost would be $3,582,625.) These costs, of course, are in addition to the cost of Programs I and II, but they are still substantially less than would pertain if Government undertook to introduce a province-wide compulsory program.

On the basis of M.S.I.'s current costs and payments we estimate that similar coverage for all residents of Saskatchewan would cost $25,043,000 (918,000 x $27.28). If we assume that a premium or tax of $17.50 per individual and $35 per family is levied, this would produce an income of $10,245,000 provided that all residents were able to pay. Thus, the net cost to the Government of Saskatchewan would be $14,798,000, plus uncollectable premiums or premiums reduced because of the financial circumstances of some applicants.

Quite frankly, we believe that the economics involved are alone sufficient to suggest that this Province should not undertake a program which in its first year will cost the Provincial Treasury at least $15,000,000. The financial position of this Province is no secret, and recent experience with the hospital plan suggests that even on the basis of shared costs, we may not be able to afford the responsibilities which the Government has already assumed. On this basis, the much more limited financial responsibility of the Plan we propose would appeal to members of the Committee and to members of the Government.

Nonetheless, it is not primarily on financial grounds that we oppose a compulsory program and favour the evolutionary, voluntary approach which we have recommended. We believe that the program which we have outlined will meet a need which exists, will provide for greater voluntary effort, is flexible, will form a sound basis for further study and possible subsequent modification, and will provide the essential support of the profession to which your Chairman has referred.

We also believe that this program meets the requirements of the five principles which the Premier of our Province has stated as necessary requisites of a sound medical care program for Saskatchewan. It is *universally available* to all persons seeking insurance coverage for the costs of medical services. Existing barriers to coverage due to age, state of health, or financial status, have been removed.

It is based on the *prepayment principle*. As such, it seeks to increase the number of persons who are using this means of securing protection. It allows the continuation of medical practice under circumstances which have led to substantial achievements in the *quality of service*. It avoids those circumstances, advocated by some organizations, which could lead to a deterioration in the quality of service.

It provides for *responsibility to the appropriate public authority for spending of public moneys* and envisages substantial Government participation both as a regulating agent and in an auditing capacity. It is in a form which is *acceptable to the doctors who are providing services*, and as it maintains the best elements of an arrangement which previously had operated to the satisfaction of many of our residents who participated in insured programs, we must conclude that our proposals would be *satisfactory to those persons receiving services*.

THE PROJECTION OF COSTS FOR HOSPITAL BEDS NEEDED IN SASKATCHEWAN

General hospital beds	*Construction*	*Operating*
Estimated need— 1300 at $15,000/bed	$19,500,000	
Operating costs— 1300 80% o/c at $20/day		$ 8,322,000
Cost of renovating present institutions	10,000,000	
Mental hospital beds		
Estimated need—200 beds in each of 11 units 2200 at $10,000/bed	22,000,000	
Raising present standards from $5.00—$16/day—4480 beds 100% o/c		17,987,200
Prince Albert— 350 beds at $16/day		2,044,000
Chronic care beds		
Estimated need— 950 beds at $10,000	9,500,000	
Operating costs— 950 at 80% at $14/day		3,883,600
Geriatric beds		
Operating costs— Raising present standards from $7—$14/day—434 beds at 100% o/c		1,108,870
	$61,000,000	$33,345,670

A PROGRAM TO EXTEND THE AVAILABILITY OF MEDICAL SERVICES INSURANCE IN SASKATCHEWAN WITH PARTICULAR REFERENCE TO DEMONSTRATED NEED

The recommendations which we have made regarding medical services insurance coverage have been presented in some detail. They presuppose, however, the introduction of detailed regulations in order to translate these suggestions into an effective program. In this document we have listed each of our major recommendations and have proposed regulations which we believe necessary for their successful implementation.

A. "Self-supporting citizens should be encouraged to ensure themselves and their families by subscribing to one of the voluntary programs of medical services insurance."

We would recommend that the following suggestions be implemented to ensure that adequate levels of protection will be available to the public and to ensure that the insurer will not differentiate against the individual purchaser or the purchaser who does not meet the usual underwriting requirements.

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We would suggest that as a requirement for licensing, each insurance carrier in Saskatchewan would agree:

1. To provide that all contracts for medical services insurance be made available on both "group" and "individual" bases on similar terms and conditions.

2. To undertake that all new contracts will not provide less than an in-hospital medical insurance coverage as a minimum level of benefits and that, preferably, a much more comprehensive range of physicians' services be included.

3. To undertake that all existing contracts will be amended to conform with this minimum level of benefits within a period of 15 months.

4. To provide that these coverages will be made available to all applicants under 65 years of age (age of the head of the household) without evidence of insurability.

5. To provide that all participants may continue their coverage (allowing for premium variations) until the participants attain the age of 65 years.

6. To undertake that the premium differential between "group" and "individual" coverage be limited to the actual difference in cost of *administering* the two types of coverage.

7. To undertake that waiting periods for new applicants be of reasonable duration and that all applications for individual coverage be accepted if they are received within pre-selected enrolment time periods.

8. To undertake that all promotional advertising be factual as to benefits and restrictions and that misleading statements be avoided.

B. "Three elements of the population require assistance from public funds to permit them to obtain the medical services insurance which they require."

Because these proposals imply the subsidy of premiums by Government, the Committee should determine those qualifications which would apply to approved carriers providing coverage for these persons. As the proposals envisage the provision of coverage on a net cost basis, there should be no sense of discrimination if relatively few carriers so qualify.

We would suggest as pertinent criteria:

1. That approved carriers must provide a "comprehensive" plan as one of the coverages generally available to the public, preferably on a "service" basis.

2. That approved carriers must operate on a non-profit basis.

3. That approved carriers must agree to periodic audits by Government auditors.

4. That approved carriers may accept Government representation on its Board of Management.

B1. "Those persons over 65 years of age whose premiums require subsidy, in order to bring the premium for their coverage down to that applicable to persons under 65 years of age."

To implement this suggestion we would recommend that:

1. Approved carriers would make available to all persons 65 years of age and over, whether new applicants or persons transferred from other carriers, the choice of a comprehensive contract, or an in-hospital medical contract, at the same premium rates, and on the same terms and conditions as apply to participants in the age group under sixty-five.

2. Approved carriers would undertake to maintain cost records of the 65-and-over participants separate from other subscribers, and the amount of subsidy required from Government would be based on the number of over-65 participants times the amount by which the per capita cost of this group exceeded the per capita cost of enrolled persons under 65.

3. For the practical purposes of record keeping, all dependants of a participant who is 65 years of age or over would qualify as "over 65's". In most instances, the sole dependant would be the wife of the participant.

4. It is possible that some persons would not wish to have their premiums subsidized in this manner. They would not be forced to participate in this arrangement, but could continue to be insured by the carrier of their choice. They would, however, be required to pay, themselves, the full premium cost.

B2. "Those persons of all ages with low incomes and limited means".

We would suggest that:

1. These persons would be asked to complete a needs test determination which would be available through their local municipal offices.

2. If on the basis of this determination an applicant was adjudged to be eligible for a full or partial subsidy of his premium, he would be provided with a document which indicated the amount of subsidy applicable.

3. The applicant would then forward this authorization to an approved carrier, together with the amount of premium for which he was personally responsible.

4. The only eligible coverage would be a "comprehensive" contract, preferably on a service basis.

5. The approved carrier would use the authorization form to bill the Government for the amount of subsidy which was applicable.

B3. "Those persons who are non-insurable at regular rates because of pre-existing medical conditions".

We do not believe that it is possible to set out an arrangement for subsidy of these premiums by Government. It is our view that:

1. Many of these persons are aged 65 and over, or would qualify for subsidy on the needs test determination.

2. It is difficult to segregate other persons in this category as many would be dependants of participants.

3. All licensed carriers should be required to accept applications from these persons, and the increased costs arising out of their participation should be reflected in the general premium rates applicable to all participants.

OTHER PROGRAMS

1. Programs I and II: We would recommend that Program I should be retained but that persons covered under Program II should be assimilated into the category of persons of all ages of low incomes and limited means.

2. The Swift Current Program: We recommend that this program be continued. We also anticipate that it would qualify as an approved carrier and as such would be eligible to receive subsidies for those persons requiring financial assistance from Government.

3. We also recommend that other programs such as the cancer program, the Workmen's Compensation Board and the antituberculosis program be continued

as separate entities, as they relate to specific areas of interest which are best administered under existing arrangements.

SUMMARY

If the Committee accepts the foregoing recommendations, we believe that it will be in a position to formulate a program which will ensure a broad insurance coverage for the residents of this province. We would commend the flexibility of these arrangements for your consideration and would advise that all members of the profession will support the implementation of these proposals.

GENERAL PRACTICE

1961 SEMINAR ON ALCOHOLISM FOR PHYSICIANS

A TWO-DAY seminar course for physicians, especially those in general practice or in public health work, is being planned under the joint auspices of the College of General Practice (Medicine) of Canada and the Alcoholism and Drug Addiction Research Foundation. The seminar will be held at the Alcoholism and Drug Addiction Research Foundation, 24 Harbord Street, Toronto, on Friday and Saturday, November 24 and 25, 1961. Attendance at the course will be limited to 25.

Attendance at this seminar qualifies members of the College of General Practice for 12 hours of Category 1 studies. The Foundation would also be prepared to provide more prolonged periods of in-service training, for one or two physicians at a time, if this should be desired.

There will be four sessions of approximately three hours each, one such session each morning and afternoon of the two days.

At each session various members of the staff of the Addiction Research Foundation will make short presentations in the nature of working papers, to be followed by discussions. A part of one session will be in the nature of a tutorial session in which small groups of three or four will meet with a particular staff member for more intensive discussion of their areas of particular interest.

Among topics to be considered will be: the nature of the problem, with reference to social background, psychopathology, physiology, organic pathology, etc.; medical management, including acute phase treatment, continuing treatment and rehabilitation, group therapy. Special problems such as the alcoholic in industry, alcoholism and tuberculosis, and family problems, will also be dealt with.

Inquiries about enrolment should be directed to Dr. John D. Armstrong, Medical Director, Alcoholism and Drug Addiction Research Foundation, 24 Harbord Street, Toronto 5, Ontario.

OBITUARIES

DR. PERCY BLAKELY MACFARLANE

AN APPRECIATION

Percy Macfarlane passed to his reward on May 19, 1961. For almost half a century his outstanding service to his profession, to his community and to his fellow men earned for him a lasting place in the hearts and minds of a great circle of friends and associates. His passing will be deeply and widely mourned.

Percy was a Canadian pioneer in his chosen specialty of ophthalmology and otolaryngology. He was early in the field in his city of Hamilton and, with the passing of his friend and mentor, the late Dr. John P. Morton, he became the dean of the growing group of specialists in Hamilton in this branch of medicine. His services to his specialty and to medicine in general were of a high order and were widely recognized.

His capacity for friendship, and for loyalty to friend and associate, was great. To know him was to love him. His fine intellect, his high principles, his taste for cultural things, and his understanding of and love of human nature endeared him to all with whom he came in contact.

We shall not soon see his like again. His family mourns the loss of a loving husband and father. His professional associates have lost a valued consultant and a true friend. His community and his fellow men will miss his kindly personality and his great contributions to their welfare.

Robert Louis Stevenson, whose tribute to the medical profession is unsurpassed in the English language, undoubtedly had in mind the physician of the type of Percy Macfarlane when he wrote:

"There are men, and classes of men, that stand above the common run . . . the physician almost as a rule . . . And when this stage of man is over and done with, and only remembered to be marvelled at in history, he will be thought to have suffered as little as any from the defects of his period, and most notably exhibited the virtues of his race."

W.J.D.

DR. MICHEL SEIGNEUR, 53, died at his home in Montreal, P.Q., on July 22. Dr. Seigneur had been president of the Jean Marie Vianney Hospital, St-Léonard de Port Maurice, and surgeon-in-chief of Notre Dame de la Merci and St-Charles Borrommée hospitals.

He is survived by his widow and four daughters.

DR. ALBERT L. WAGNER, 68, former medical health officer in Elmira, Ont., died at his home on July 17. Dr. Wagner graduated in 1918 and opened his first and only practice the following year in Elmira. He practised there for 42 years. He had served overseas during World War II with the Royal Canadian Army Medical Corps.

He is survived by his widow and one son.

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PUBLIC HEALTH

SUMMARY OF REPORTED CASES OF NOTIFIABLE DISEASES IN CANADA*
ISSUED BY THE PUBLIC HEALTH SECTION, DOMINION BUREAU OF STATISTICS

Disease	*Week ended (1961):* June 24	July 1	July 8	July 15	*Cumulative total since beginning of year* 1961	1960
Brucellosis (Undulant fever) (044)	—	5	—	1	67	65
Diarrhea of the newborn, epidemic (764)	1	2	2	—	50	31
Diphtheria (055)	2	—	—	3	42	20
Dysentery (045, 046, 048)	81	29	45	76	1,649	1,598
(a) Amebic (046)	—	—	—	—	4	1
(b) Bacillary (045)	22	15	9	22	846	1,406
(c) Other and unspecified (048)	59	14	36	54	799	191
Encephalitis, infectious (082.0)	—	1	1	1	3	—
Food poisoning: (049.0, 042.1, 049.2)	16	9	12	3	572	770
(a) Staphylococcus intoxication (049.0)	—	—	—	—	20	309
(b) Salmonella with food as vehicle of infection (042.1)	15	7	12	3	547	444
(c) Unspecified (049.2)	1	2	—	—	5	17
Hepatitis, infectious (including serum hepatitis) (092, N998.5)	145	159	251	128	5,878	3,150
Meningitis, viral or aseptic (080.2, 082.1)	3	2	6	8	100	123
(a) Due to poliovirus	—	—	—	1	6	38
(b) Due to Coxsackie virus	—	—	—	—	5	17
(c) Due to ECHO virus	—	—	—	—	—	2
(d) Other and unspecified	3	2	6	7	89	66
Meningococcal infections (057)	1	2	2	2	74	106
Pemphigus neonatorum (Impetigo of the newborn) (766)	—	—	—	—	9	7
Pertussis (Whooping cough) (056)	92	108	91	26	2,253	3,095
Poliomyelitis, paralytic (080.0, 080.1)	5	3	2	1	44	252
Scarlet fever and Streptococcal sore throat (050, 051)	208	150	109	114	8,852	15,871
Typhoid and Paratyphoid fever (040, 041)	2	5	6	12	142	187
Venereal diseases: (020-039)	311	350	326	263	9,423	9,082
(a) Gonorrhea (030-035)	266	316	297	235	8,253	8,010
(b) Syphilis (020-029)	45	34	29	28	1,169	1,069
(c) Other† (036-039)	—	—	—	—	1	3

*Figures for the Yukon are received four-weekly and are, therefore, shown in the cumulative totals only.
†Including chancroid, granuloma inguinale and lymphogranuloma venereum.

BOOK REVIEWS

RELIEF OF SYMPTOMS. 2nd ed. Walter Modell. 374 pp. The C. V. Mosby Co., St. Louis, Mo., 1961. $11.50.

This is a clearly written, concise and practical guide to the use of drugs for symptomatic relief. The general objectives and arrangement of the book are rather similar to those of the first edition. The first section deals with various theoretical aspects of symptomatic, as opposed to specific or etiologic therapy, and with the complex problems involved in their combined use, which is essential for "full" treatment of the patient. The author emphasizes the need of assessing prior to start of treatment both the symptoms (changes related to the disease) and the complaints (patient's testimony of symptoms). Emphasis is also placed on such questions as (a) selection of the appropriate drug, (b) tailoring the dose to fit the patient, (c) determining whether the effects following administration are "due to the medication, to the medicating or to the medicator", and (d) problems involved in treating ambulant and hospital patients. The nature of placebo action and various aspects of both medicinal and non-medicinal placebo effects are also discussed. In the second section of the book, dealing with practice, treatment of all of the more commonly met symptoms is considered, and in principle non-proprietary names are used throughout the text. The various drugs available for treatment of each of the symptoms are also conveniently tabulated, usually in order of effectiveness.

The final section of the book deals with the dangers associated with the indiscriminate use of cortisone, ACTH and related hormonal preparations, which by their influence on fundamental biologic processes, not only mask symptoms but lead to serious systemic effects. It is concluded that these drugs should rarely be used for symptomatic relief alone, but only for the prevention of undesirable adaptive reactions.

Although the book contains nothing new and revolutionary, it embodies a great many useful practical points regarding drug therapy based on the long experience of the author as a clinical pharmacologist. It should be a valuable aid to both the practising physician and to more advanced medical students.

HEREDITY IN OPHTHALMOLOGY. Translated from the French edition by Jules François. 731 pp. Illust. The C. V. Mosby Co., St. Louis, Mo., 1961. $23.00.

The first two sections of this book discuss general genetics and genetics in ophthalmology. In these sections the types of inheritance, mutation, the various manifestations of gene inheritance, statistics and biometry of heredity are described. There is a chapter on the prevention and treatment of hereditary diseases of the eye.

The third section comprises the larger body of the book and takes up, in order, the various ocular diseases which are of hereditary nature. Of particular interest is the discussion of the heredity of colour blindness. The final section of the book covers general diseases which are hereditary in nature and which cause ocular change.

This is a most valuable book, particularly as a compilation of the various ocular diseases which are of hereditary origin. The author has surveyed the literature carefully and has chosen his discussion and the illustrations with wisdom. As a result, the book is easy to read, the illustrations are valuable and the material is informative.

The volume is well bound and printed clearly on good paper, and the illustrations are most satisfactory. The book should be in the possession of all ophthalmologists and geneticists who are interested in hereditary diseases of the eye.

RECOGNIZING THE DEPRESSED PATIENT. With Essentials of Management and Treatment. Frank J. Ayd, Jr. 138 pp. Grune & Stratton, Inc., New York; The Ryerson Press, Toronto, 1961. $4.00.

This book appears to be an expanded version of an article "Recognizing the Depressed Patient" by the same author, which appeared in the *Current Medical Digest*, XXIV, No. 10, October 1957. Reprints of this have already been widely distributed through the mail by one of the drug companies. The book is primarily intended for non-psychiatrists and has, perhaps as a result of this, both weaknesses and strengths. The chapters on the signs and symptoms of depression which are arranged under physical, emotional, and psychic symptoms, are simply but carefully written and could be read with benefit by many psychiatric specialists. The chapter on suicide and homicide also contains much useful information.

Even in these chapters, however, the lack of bibliography is an obvious shortcoming to the interested reader. Some of the other chapters, especially those dealing with the causes and conditions of depression, and with treatment, are, in the opinion of this reviewer, so over-simplified as to be somewhat misleading. For instance, many psychiatrists would disagree with the author's statement on page 7 that electroshock therapy as a method of treatment for depression "was successful irrespective of the presumed psychological cause of the depression".

In fact, this volume raises the problem of books for non-specialists written by specialists. It is a frequent shortcoming of such books that so much controversy and subtlety must be omitted that serious inaccuracies may result. In the present volume the chapter on therapeutics illustrates this point. The author does not define adequately the clinical states which he calls "improved" and furthermore (and this is perhaps a more serious criticism) he omits any discussion of placebo-effect.

CIRCULATORY ULCERS: A PHYSICAL APPROACH. Hilton G. Tranchell and Charles R. Bannister. 91 pp. Illust. John Wright & Sons Ltd., Bristol; The Macmillan Company of Canada Limited, Toronto, 1960. $5.00.

This 91-page book discusses in detail the treatment of circulatory ulcers from the point of view of the physiotherapist. The commonly encountered chronic ulcers are classified and their causation is explained for the benefit of the student physiotherapist. A methodical description of the various treatments is included, covering the use of ultraviolet light, infrared, ultrasound, massage, exercises, types of bandages, as well as various topical medications. Emphasis is placed on the meticulous day-to-day examination of the lesion and reassessment of the treatment, with suitable variations of the physical treatments in relation to the stage of healing of the ulcer. Usually the rationale and basic considerations for the various treatments are explained briefly and the commonly employed surgical measures are described with continuing emphasis on the proper regimen of preoperative and postoperative care and the obvious need for close co-operation between the surgeon, physiotherapist, nursing service and the patient. This book has been written for the student physiotherapist and there is considerable repetition of the principles and techniques of treatment in several chapters. However, this does not detract from the value of the book, considering its intended purpose. Some of the illustrations do not add much to the understanding of the subject.

This text should have a useful place in physiotherapy departments and surgical clinics and would be interesting to any physician or surgeon who wishes to read a comprehensive discussion of the careful use of physical methods in the treatment of circulatory ulcers.

RADIOGRAPHIC ANATOMY OF THE HUMAN SKELETON. A Handbook for Radiographers. W. H. Johnson and J. A. Kennedy. 280 pp. Illust. E. & S. Livingstone Ltd., Edinburgh; The Macmillan Company of Canada Limited, Toronto, 1961. $8.50.

In their preface the authors say that they have long felt that there is a need for a concise textbook of osteology for students of radiography. It is within the confines of this premise that the merits of this book lie.

The title on the cover indicates that it is a text of radiographic anatomy of the human skeleton. One might take this to indicate a more elaborate treatise than is contained within. The sub-title, however, reveals that it is "A Handbook for Radiographers". As such it is an excellent work.

A thorough basic knowledge of skeletal anatomy is a fundamental factor in good radiographic positioning and technique. A technician in possession of such knowledge has a sound foundation from which to become proficient in the radiography not merely of skeletal structures but of the entire body.

This book should certainly provide the student technician with such a foundation. It is well and simply written and is profusely and clearly illustrated. The diagrams and drawings are excellent and of a higher standard than is usually encountered in textbooks for technicians. The accompanying radiographs likewise are well chosen and of a generally high standard.

The book is one that can most certainly be recommended for the technician. Student radiologists also might well benefit from a reading of it, although it is not primarily intended for them.

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ANNUAL REVIEW OF MEDICINE. Vol. 12. Edited by David A. Rytand and William P. Creger. 455 pp. Annual Reviews, Inc., Palo Alto, California, 1961. $7.50.

This volume again covers a wide scattering of basic medical problems and very practical clinical subjects. There is a definite trend to choose a fairly narrow aspect of a subject and go into it in some depth. The result is a scholarly, critical appraisal of present knowledge. The discussion is broader than in a journal article and yet more up to date and usually more detailed than in a textbook. The references are excellent. The result is the sort of grasp of a subject one would like to acquire oneself, but of course it is impossible to have the time to do the reading, thinking and synthesis that these specialists, each in his own field, have done. For example, in an article on kidney disease, only acquired tubular disorders with particular reference to disturbances of concentration, dilution, and acid base regulation are discussed. The review becomes quite fundamental, but it is both interesting and good for a clinician to be exposed to this.

The discussion on virus diseases is confined to the respiratory system. It would be extremely rewarding to the general practitioner, for it points out that 70 new viruses have been described in the last ten years, which helps us to rationalize our trouble in keeping up with them. One virus can cause a broad spectrum of disease in different individuals; in particular, the differences between infants and adults in their response to the same virus are emphasized. Conversely, the identical clinical picture can be caused by a group of viruses. The hazards and difficulties in associating a virus with a disease in the first place are emphasized, as well as the problems posed in diagnosis of individual cases. Any who have felt that antibiotics may affect some virus diseases will be interested to see that the Eaton agent, which is responsible for cases of primary atypical pneumonia with cold hemagglutinins, is said to be susceptible to aureomycin and streptomycin. Another article on "untoward reactions to antimicrobial agents" is very timely.

The section devoted to the physiology of the surgically altered stomach presents a most worthwhile review of what is accomplished by the various operations that have enjoyed a vogue in the ever-changing fashions of surgical treatment of peptic ulcer. The article on the oral hypoglycemic agents, by Alexander Marble, comes at an appropriate time, when there seems to be a pause in the introduction to this field of drugs that are new in their mechanism or basic derivation, and yet after sufficient time has elapsed to obtain a realistic perspective concerning those agents of this type that have been introduced in the past.

This is an excellent volume to draw from the library to consult those chapters which particularly cover one's individual fields of interest.

L'HYPNOSE. Les problèmes théoriques et pratiques. La technique. 2nd ed. L. Chertok. 143 pp. Masson & Cie, Paris, 1961. 24 NF.

The author of this volume is a well-recognized and highly respected worker in the fields of psychosomatic medicine and hypnosis. This pattern of interest and investigation, which had its start in Canada some twenty years ago, had spread to the United States and from there to other countries throughout the world. Very little has been published about this subject in France during the past 50 years. The study of hypnosis reached its zenith in that country by the end of the last century and then receded into complete oblivion. The vast research in hypnosis and its application in medicine carried out in the United States and Russia prompted the author to summarize these findings for dissemination in France. Within the limits of this small book he has succeeded admirably.

The first edition published in 1958 dealt with the rise and fall of hypnosis in France. The second and revised edition contains theoretical and practical considerations as developed in the U.S.A. and the U.S.S.R. Since existing theories do not explain hypnosis fully, the author clarifies the theoretical considerations under three headings in three chapters: (1) Theories developing from experimental psychology; (2) Theories developing from Pavlovian conditioned reflex studies; (3) Theories based on psychoanalytic concepts.

Of interest to American investigators are references to obstetrical hypnotaria in Russia where painless childbirth under hypnosis has been carried out for the past 25 years and has been reported in their literature since 1938. Hypnodrama based on the psychodrama of Moreno is also of interest, since the use of hypnosis in psychodrama for therapy has received more attention in European countries than it has in America.

In general, this edition covers the subject of hypnosis briefly but with excellent discrimination. It is recommended not only for beginners but for the more experienced as a review and for reorientation.

American publishers would do well to imitate, if not in fact improve on, the excellent layout and printing of this little volume.

THE ENCYCLOPEDIA OF MICROSCOPY. Edited by George L. Clark. 693 pp. Illust. Reinhold Publishing Corporation, New York, 1961. $25.00.

Like most encyclopedias written by multiple authors, this book is very uneven. The articles range from a copy of a short commercial brochure on the general principles of fluorescence microscopy to the results of applied microscopy in one particular field (kidney ultrastructure). Again, as in most encyclopedias, the information available on any one subject is not adequate as a guide if one knows nothing about it to begin with, but seems superficial if one has had experience in the field. The composer of the blurb on the dust jacket awakens our distrust by calling the book an extraordinary scientific achievement. However, apart from these standard disabilities of an encyclopedia the book does bear out the final paragraph on the dust cover. "Here in one convenient volume, is the most extensive and important collection of information ever published on microscopy."

Few of us could be aware that it is possible to write on 26 types of microscopy. Light waves tampered with in every way, x-rays, sound rays, the electron and the proton—all forms of energy which if focusable can throw enlarged images—are all catalogued here together with many of their applications, some fascinating illustrations, good sections on the history of the various types of microscopy and references for further reading.

Physicists, mineralogists, chemists, biologists and textile workers will all find something interesting about their trade and much that is even more interesting about each other's. This is a recommended reference book.

FOR SALE, eye and nose and throat practice; Doctor wishes to retire, ground floor office, 5 rooms, centre of medical district of Peterborough, Ont. Reply to Box 8, CMA Journal, 150 St. George Street, Toronto 5, Ont.

Residencies and Internships

FIRST YEAR RESIDENT IN OB-GYN, starting immediately or January 1, 1962. Stipend and maintenance. Canadian schools or certified by ECFMG. Write Paul O. Funk, M.D., Director of Medical Education, Saint Ann Hospital, 2475 East Boulevard, Cleveland 20, Ohio, U.S.A.

PSYCHIATRIC RESIDENCIES.—Hospital with large medical staff offers fully accredited three-year training program beginning July 1, 1962 for men and women graduates of Canadian or American schools desiring certification in psychiatry. Includes postgraduate course, guest lectures, training in modern therapeutic procedures and supervised work in mental hygiene clinics. Liberal salary includes family maintenance. Reply to Box 603, CMA Journal, 150 St. George Street, Toronto 5, Ont.

STATE OF CONNECTICUT, FAIRFIELD STATE HOSPITAL, NEWTOWN, CONN., U.S.A.—Residents in psychiatry. Applications are invited from men and women graduates of Canadian medical schools for residency training in psychiatry. Large modern hospital with three-year training accreditation for American board certification. Active and varied teaching program in affiliation with Yale University. Close to metropolitan areas. Maintenance at nominal cost immediately available for single applicants, waiting list for family accommodations. Beginning stipend $455. per month. Write giving particulars to Jane E. Oltman, M.D., Director of Training.

GENERAL HOSPITAL. St. John's Newfoundland, Canada. Applications are invited to fill vacancies on the intern staff of the General Hospital, St. John's, Newfoundland. This 456-bed general hospital is approved for intern training by the Canadian Medical Association. Salary is at the rate of $300 per month, less a deduction of $47 per month for room and board. An additional allowance of $50 per month is payable to married applicants with one or more dependents residing in St. John's. Transportation is provided from Canadian centres on the basis of one year's service. Further information can be obtained from the Superintendent, The General Hospital, St. John's, Nfld.

GENERAL HOSPITAL, St. John's, Newfoundland, Canada. Applications are invited from interested physicians to fill residency posts for postgraduate training commencing January 1, 1962. These are approved by the Royal College of Physicians and Surgeons of Canada. This is a 456-bed acute general hospital, with positions available in medicine, surgery, pediatric, radiology, pathology and anesthesia. Salary is $4000 per year. An allowance of $50 per month is payable to residents with dependents residing in St. John's. Transportation is provided from Canadian and U.K. centres. For further information please contact: The Superintendent, The General Hospital, St. John's Newfoundland, Canada.

WESTERN CANADA.—Resident and assistant-residents in diagnostic radiology required January 1, 1962 and July 1, 1962. 800-bed hospital. All forms of standard and specialized radiological procedures. Active teaching unit. Stipend $400 monthly for resident and $300 for assistant. Training fully recognized by Royal College of Physicians and Surgeons of Canada. Applications to Director of Radiology, Regina, General Hospital, Regina, Sask.

PATHOLOGY RESIDENCY.—4 year approved program in pathologic anatomy and clinical pathology supervised by four pathologists, two biochemists and bacteriologist. 710-bed hospital, over 6000 surgical and 400 autopsies. Opportunities for research in ultra-micro chemistry and new diagnostic methods; animal research facilities under construction. Apply: Edwin M. Knights, Jr., M.D., Pathology Department, Hurly Hospital, Flint 2, Michigan, U.S.A.

RESIDENT IN ANESTHESIA WANTED JANUARY 1, 1962, for the recently reconstructed 270-bed Queen Elizabeth Hospital of Montreal. Approved for postgraduate training by the Canadian, American and British authorities. Stipend varies with the experience of the applicant from $200 to $300 per month, plus room and board or living-out allowances. Apply to Dr. W. G. Cullen, Anesthetist-in-Chief, 2100 Marlowe Avenue, Montreal 28, Quebec.

A 350-BED GENERAL HOSPITAL offers rotating internship with full teaching program in all services. Remuneration $250 per month and full maintenance. Apply to Director, Medical Education and Research, The Doctors Hospital, 45 Brunswick Ave., Toronto, Ont.

ST. THOMAS-ELGIN GENERAL HOSPITAL.—Resident junior rotating interns. Salary $250 per month less $75 per month for full maintenance. Passage money can be advanced as loan, if required; to be deducted from salary over 12 month period. Half of passage money will be refunded at end of one years' employment. Foreign applicants must possess the Permanent Educational Council for Foreign Medical School. Hospital opened 1954 is a fully accredited 382-bed general hospital and is fully approved by the Canadian Medical Association for intern training. Apply Superintendent, St. Thomas-Elgin General Hospital, St. Thomas, Ont.

Canad. M. A. J.
Sept. 9, 1961, vol. 85

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ANESTHETISTS' MEETING IN KINGSTON, ONT., OCTOBER 6 AND 7

The fall meeting of the combined Section of Anaesthesia of the Ontario Medical Association and the Ontario Division of the Canadian Anaesthetists' Society will be held in Kingston, Ont., on October 6 and 7, 1961. The guest speakers will include Dr. Jay Jacoby and Dr. David Power.

This meeting will follow immediately after a refresher course in anesthesia for general practitioners which will be held on Tuesday, October 3, Wednesday, October 4, and Thursday, October 5.

SECOND CANADIAN MENTAL HEALTH SERVICES INSTITUTE

The Second Canadian Mental Health Services Institute, sponsored by the Canadian Psychiatric Association, will be held at the Château Laurier, Ottawa, from January 15 to 18, 1962. The theme of the Institute will be "Mental Health Services for Canada—Examination of the 1961 C.M.H.A. Report". For further information, write to: Dr. V. E. Chase, Chairman, Planning Committee, c/o Canadian Psychiatric Association, Suite 103, 225 Lisgar Street, Ottawa, Ont.

AMERICAN THORACIC SOCIETY ANNUAL MEETING

The American Thoracic Society invites submission of abstracts of papers relating to the general field of tuberculosis and other respiratory diseases for presentation at its 57th Annual Meeting to be held in conjunction with that of the National Tuberculosis Association in Miami Beach, Florida, May 20-23, 1962. Abstracts must be in the hands of the program committee not later than January 5, 1962. Eight copies should be submitted. Each abstract should be limited to 300 words. Further information regarding the submission of abstracts may be obtained by writing Asher Marks, M.D., Chairman of the Medical Sessions Committee, American Thoracic Society, 1790 Broadway, New York 19, N.Y.

CHANGING CLINICAL PICTURE OF DIGITALIS INTOXICATION

Twenty-four cases (14 women and 10 men) of digitalis intoxication diagnosed during a 12-month period on the basis of stated criteria were analyzed by Soffer (*A.M.A. Arch. Int. Med.*, 107: 681, 1961). Nine cases (37%) were characterized electrocardiographically by atrioventricular dissociation with an AV nodal rate above 70 per minute.

It is noted that recent emphasis on paroxysmal auricular tachycardia has unwittingly obscured the fact that non-paroxysmal auricular tachycardia is a more frequent and more valuable clue to the early diagnosis of digitalis intoxication.

Twenty cases (83%) were induced by digoxin; this finding demonstrates that a "safe" rapidly excreted purified glycoside, such as digoxin, can readily produce intoxication. Toxicity occurred on

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initial digitalization only if the administration was parenteral, suggesting that "standard dosages" for parenteral digitalization with digoxin may often be precariously close to the toxic range.

The average age of the 24 patients in this series was 69.7 years; this finding would indicate that the ageing patient with a diseased myocardium is the most likely candidate for digitalis intoxication and that attempts to administer average amounts of digitalis may lead to aggravation of the clinical condition.

Nineteen patients (79%) were on potent potassium-losing diuretics (chlorothiazide or mercurial diuretics) which often precipitate the appearance of toxicity, but serum potassium determinations proved to be of little assistance in prophylaxis or diagnosis.

Intravenous monopotassium glutamate appeared to be less hazardous than other intravenous potassium salts in the treatment of digitalis intoxication. There are, however, many patients for whom potassium (except perhaps monopotassium glutamate) and digitalis are contraindicated until other measures relieve to some extent the degree of cardiac decompensation.

AMERICAN PSYCHOSOMATIC SOCIETY

The 19th Annual Meeting of the American Psychosomatic Society will be held at The Sheraton Hotel in Rochester, New York, on Friday, Saturday, and Sunday, March 30, 31, and April 1, 1962.

The Program Committee will welcome abstracts or original work to be presented at the meeting by members or non-members of the Society. Abstracts should be not more than two typewritten pages, and should be submitted in eleven copies. The deadline for submission is December 1, 1961.

Abstracts should be addressed to Dr. Stewart Wolff, Program Committee, 265 Nassau Road, Roosevelt, N.Y.

INOCULATION OF HUMAN VOLUNTEERS WITH VIRUS FROM A COMMON COLD

Fifty-four volunteers were inoculated, by various routes, with pooled nasal washings of a patient with a typical cold, containing H.G.P. virus. Colds were induced in 16 volunteers, who were mainly those who had received virus as nasal washings, but also in two of seven volunteers who had been given the virus by nasal swabbing, and in two of seven who had received it by conjunctival swabbing.

It appeared that the throat might be relatively resistant to infection since no colds were induced in volunteers who had received virus by means of throat swabs. In those patients in whom colds were induced by virus administered on conjunctival swabs, there were no signs or symptoms localized to the eye, nor was virus recovered from the conjunctiva. Virus was isolated most readily in nasal washings, and mainly from those with colds.

Bynoe *et al.* (*Lancet,* 1: 1194, 1961) found a correlation between low levels of serum antibody and the development of colds: of 21 volunteers with antibody level be-

low K = 0.22, 14 developed colds. Therefore, circulating antibody may protect against disease, and vaccination might be an effective method of prophylaxis. However, some volunteers with low antibody levels did not become infected, and it is suggested that there may be some non-specific resistance to infection. Significant rises of antibody level were found during the illness in 11 of 15 volunteers with colds, but also in 3 of 32 volunteers without colds.

HYPERCHOLESTEROLEMIC XANTHOMATOSIS

Jepson (*Brit. M. J.*, 1: 847, 1961) studied 15 patients with familial hypercholesterolemic xanthomatosis and three patients with idiopathic hyperlipemia, treated with a diet in which the normal fat was replaced by artificial "milk", "margarine", and "cheese" containing a high proportion of an unsaturated fat (corn oil). At the end of the "control" and "treatment" periods, each of which lasted for four months, clinical manifestations were evaluated; estimations of blood cholesterol (total and free), phospholipids, total fatty acids and triglycerides, and of plasma turbidity were carried out; and measurements were made of blood clotting and fibrinolysis time. Venous occlusion plethysmography measurements of peripheral circulation were also recorded. During this study the patients continued at work; they found the diet palatable and tolerated it well.

Favourable results from this regimen were reported. The blood cholesterol (total and free), phospholipids and plasma turbidity were reduced significantly; the triglycerides were also reduced in some cases. Xanthomata decreased in size, particularly xanthoma tuberosum, which often disappeared. The blood clotting and fibrinolysis time were altered in most cases in a manner presumably beneficial to the patient. Among the six patients with angina, there was no clinical or electrocardiographic evidence of improvement in myocardial ischemia; in three of the six patients with intermittent claudication, symptoms decreased, but there was no improvement in the peripheral circulation of the foot as measured by plethysmography.

In hypercholesterolemic xanthomatosis the incidence of atherosclerosis is high and the prognosis poor when myocardial ischemia or peripheral vascular disease developed. Results of this study indicate that a diet such as that used by these patients forms a practical method of treatment and is worthy of a trial in the hope of preventing further manifestations of atherosclerosis.

CHRONIC PULMONARY BERYLLIOSIS IN A FEMALE CHEMIST

A chronic progressive granulomatous disease of the lungs is reported by McCallum, Rannie and Verity (*Brit. J. Indust. Med.*, 18: 133, 1961) in a female chemist who had worked for approximately two years with a beryllium compound in the manufacture of fluorescent lighting tubes. The level of beryllium in the laboratory atmosphere

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A NEW ERA IN ANTICOAGULANT THERAPY ...LONG-TERM MAINTENANCE

"Not only will patients live longer on long-term anticoagulant therapy, but they will on the whole lead a fuller and more comfortable existence."

Extensive experience over the past ten years has demonstrated the value and practicality of *long-term* anticoagulant therapy in selected cases of myocardial infarction and related disorders, to prevent thromboembolic episodes and extend life expectancy.[1-6]

Friedberg,[2] in his survey covering 3,254 cases, has pointed out that *mortality is reduced* at least one-third to one-half and that when anticoagulant therapy is properly administered under controlled conditions, *major hemorrhage is rare.*

A decade of experience with "Danilone" (phenylindanedione) has shown that this anticoagulant is effective, safe, and economical in long-term use, providing one of the cornerstones of successful anticoagulant therapy.

For a free copy of the new 16-page *Report on the Increasing Practicality of Long-Term Anticoagulant Treatment*, write to the Medical Department, Charles E. Frosst & Co., P.O. Box 247, Montreal 3, Quebec.

ORIGINAL "Frosst" CONTRIBUTION TO WORLD-WIDE ANTICOAGULANT THERAPY

"DANILONE"

(Brand of Phenylindanedione Tablets)

Supplied: **50 mg.** (white—scored) **25 mg.** (yellow—scored)

"*... more easily controlled, much less expensive ... the long-term anticoagulant of choice.*"

Oliver, M.F.: Brit. M.J. **1**:1176, 1959

DOSAGE: INITIAL DOSAGE varies over a wide range. The most frequently recommended initial dose is 200 mg. divided into two doses 12 hours apart. Some authors have found that, in about 50% of cases, 500 to 600 mg. may be required in the first 24 hours.[7] Such large doses should be used with caution and avoided in patients with congestive heart failure and in those over 65 years of age. MAINTENANCE DOSAGE also varies over a wide range—between 25 and 250 mg. daily being required. *Bottles of 100.*

CAUTION: If hemorrhage occurs, the drug should be withdrawn immediately and, when necessary, 25 to 50 mg. of vitamin K_1 should be administered. Sensitivity reactions (skin rash, pruritus, diarrhea, agranulocytosis, fever, jaundice) have occurred but they are very rare. In cases where the urine is alkaline, it may become orange-red in colour due to the excretion of alkaline salts of "Danilone" or its metabolites. This colour reaction should not be mistaken for hematuria.

Also available: "DICUMAROL" (brand of bishydroxycoumarin U.S.P.) in 50 mg. and 100 mg. tablets, bottles of 100.

1. Connell, W.F.: Canad. M.A.J. **76**:664, 1957. 2. Friedberg, C.K.: New York J. Med. **58**:877, 1958. 3. Stephens, C.A.L., Jr.: Arizona Med. **17**:499, 1960. 4. Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council: Brit. M.J. **1**:803, 1959. 5. Manchester, B.: Ann. Int. Med. **47**:1202, 1957. 6. Nichol, E.S. *et al.*: Am. Heart J. **55**:142, 1958. 7. Beamish, R.E. and Carter, S.A.: Canad. M.A.J. **74**:39, 1956.

QUALITY PHARMACEUTICALS
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was found to be 2.7 μg. per cubic metre, and that in the other parts of the factory, up to 39.1 μg. per cubic metre.

The patient's symptoms began about two years after she had left this work, and she died three years later. A diagnosis of chronic pulmonary berylliosis was made during life on the basis of the combination of typical radiological changes, clinical course of the disease, and an occupational history of exposure to a beryllium compound. The diagnosis was confirmed by lung biopsy when, early in the course of the disease, a large cyst attached to the right middle lobe was removed by thoracotomy.

The clinical course of the disease was characteristic. Pulmonary function tests showed a low arterial oxygen saturation at rest and a normal pCO_2 in spite of marked hyperventilation. Both elastance and resistance of the lungs were greater than normal, and the total work of breathing was six times that of the normal. Pregnancy in this patient was associated with relief of symptoms which was maintained for some months after a normal delivery. The patient died in acute right heart failure approximately seven years after exposure to beryllium ceased.

At necropsy, beryllium was detected in the lungs chemically and was demonstrated in histological sections by special stains. Microscopically, the lung showed conchoidal bodies and doubly refractile crystals.

It is suggested that there is a sensitivity reaction to beryllium in which it is probably combined with protein to form an antigen and that the breakdown of necrotic foci provokes further reaction in the lungs with the repeated appearance of new lesions.

FAT MALABSORPTION IN CONGESTIVE CARDIAC FAILURE

The frequency of steatorrhea in 20 patients in cardiac failure was assessed by Jones (*Brit. M. J.*, 1: 1276, 1961). In 17, cardiac failure, as judged by jugular venous pressure, was present during the investigation; in the other 3, the venous pressure had fallen to normal three to seven days before the tests were begun. Patients re-

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ceived a normal ward diet. After an oral dose of 10 μc. of I^{131}-labelled triolein in 10 g. of arachis oil, the fecal output of radioactivity was measured and expressed as a percentage of the dose received by the patient; in most cases fecal total lipids were also measured.

Fat malabsorption was demonstrated in three out of the 17 patients with congestive cardiac failure: two patients had both high fecal fat and high fecal radioactivity, and one had high fecal fat but normal radioactive fat excretion. Fat malabsorption might have been present in two more cases, in both of which a high output of fecal radioactivity co-existed with a normal fecal fat excretion. No correlation of fat malabsorption with cause or chronicity of cardiac failure, loss of weight, or digitalis therapy emerged. The serum bilirubin level was slightly raised in three of the four patients with steatorrhea in whom it was measured; the possible significance of this finding is discussed by the author.

SIXTEENTH ANNUAL SYMPOSIUM ON FUNDAMENTAL CANCER RESEARCH

"Conceptual Advances in Immunology and Oncology" will be the subject of the Sixteenth Annual Symposium on Fundamental Cancer Research, to be held March 1, 2 and 3, 1962, at The University of Texas M. D. Anderson Hospital and Tumor Institute.

The three-day program will be divided into morning sessions from 9.00 a.m. to 12.00 noon and afternoon sessions from 3.00 p.m. to 6.00 p.m. Titles of the sessions are: "Theories of Antibody Production", "Metabolic Control of Antibody Synthesis", "Genetic Basis of Immune Response", "The Nature of the Antigen-Antibody Reaction", "Transplantation and Immunological Tolerance" and "Cancer Specific Antigens".

Further information on the meeting may be obtained from the Publications Department, The University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston 25, Texas, U.S.A.

EASIER HOUSEKEEPING REDUCES INCIDENCE OF TUBERCULOSIS

Modern household conveniences have been a boon to women in reducing the incidence of tuberculosis among them as well as in lightening household chores.

Such is the partial explanation of a greater decrease in tuberculosis among women over 30 than in men of the same age, as advanced by two New York State epidemiologists in a recent issue of *The American Review of Respiratory Diseases* (84: 217, 1961).

The authors, Julius Katz and Solomon Kunofsky of the New York State Department of Health, Albany, attribute to environmental factors the major role in determining trends of tuberculosis morbidity and mortality.

"The consistently lower incidence of tuberculosis among women more than 30 than men of similar age," they state, "is probably due to more pronounced improvements in environmental conditions for females. For example, while working conditions during the past 50 years have improved for both sexes, legal regulations of working conditions for women are stricter than for men. Certainly, the burden of housework has been greatly lessened during the past half century."

The conclusions of the authors on the effect of environment on the incidence of tuberculosis was reached following a study among patients of all ages of both sexes living in institutions of the New York State Department of Mental Hygiene, where living conditions were practically identical for all the patients. Not only was there a decrease in incidence at all ages but the rate of decrease was similar for men and women whereas the decrease in morbidity in the general population for upstate New York was much less for the older ages.

Contending that antimicrobial drugs in the past 15 years have "merely accentuated the rate of reduction of an already decreasing mortality," the authors credit improved living conditions for the decrease in tuberculosis morbidity during the 20th century. With less tuberculosis, it followed there were fewer deaths from the disease. A state of equilibrium between cases

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and deaths had almost been reached prior to the advent of chemotherapy, according to the authors. "The introduction of drugs upset this equilibrium by increasing the rate of inactivation of the disease and reducing the number of deaths."

MORE ON TRAFFIC ACCIDENTS

In the May 6, 1961 issue of the *Medical Journal of Australia*, Dr. R. A. Money presents an excellent review of the problems of road safety and of traffic accidents and their prevention.

Statistics show that the automobile is a greater cause of injury and death than even war, and that it is the greatest killer in the 1-35 year age group, not excluding any of the many serious diseases to which this group is liable.

Excessive speed is by far the greatest cause of fatalities; then come carelessness and inattention amongst drivers; many of whom may have neuropathic or psychopathic personalities. In 50% of fatal accidents the driver has had alcohol in some form prior to the accident; in 30% the driver has been reckless; and in 20% the blame may be laid upon the driver's falling asleep, taking a fit, suffering from diabetes, a heart attack, drug dependence, or an emotional disturbance. Only a very few fatalities can be blamed upon mechanical failure.

Actual causes of death are, first and foremost, head injuries which account for 70% of fatalities; next come injuries of the chest and abdomen; and lastly come those of the limbs.

The physician's role is essentially one of prevention: prevention of accidents; prevention of injuries when accidents occur; and prevention of permanent disability and of death when injuries occur. The advocated accident preventive measures are concerned with roads, speed limits, drivers, and motor vehicles. The design of roads to prevent accidents is concerned with the features of controlled access, type of surface, adequate lighting, avoidance of long, straight, monotonous stretches, and avoidance of flicker and of glare. Speed limits, both maximum and minimum, are necessary, but even more necessary is the strict enforcement of these limits.

The design of motor vehicles should also be an important factor in the prevention of accidents, but at present their design is more concerned with style and economy than with safety. While some progress towards greater safety is being made in some features, new hazards are being added in others. For example, the new rear-engine automobiles are economical and effective, but at certain times the road-holding qualities of the vehicle may be affected, and certainly, if a head-on collision occurs, the lack of protection from the engine may well be the deciding factor in producing one or more fatalities.

Technical safety features which should be, and easily could be, included in the design of automobiles are: more easily controlled steering mechanisms, better road-holding qualities, lower centre of gravity and non-glare head-lights. The modern tail-lights are often unnecessarily huge and may cause

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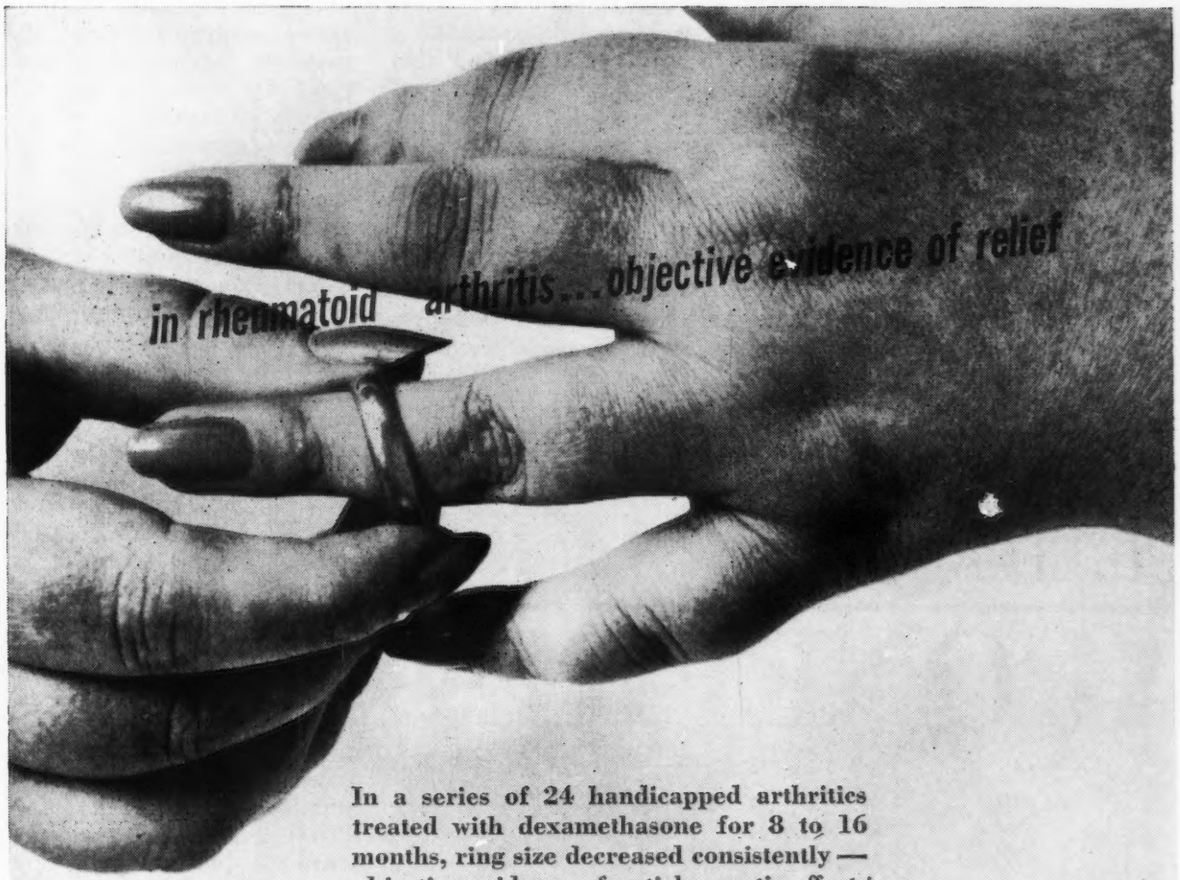

In a series of 24 handicapped arthritics treated with dexamethasone for 8 to 16 months, ring size decreased consistently — objective evidence of antirheumatic effects which were maintained throughout the entire period of observation. Improvement was also noted in other antirheumatic indices, i.e., pain on motion, tenderness, swelling and morning stiffness.[1]

Supplied: as 0.75 mg. and 0.5 mg. scored, pentagon-shaped tablets in bottles of 30, 100 and 500. Also available as Injection DECADRON* Phosphate. Additional information on DECADRON is available to physicians on request.

Reference: 1. Bunim, J. J., in Hollander, J. L.: Arthritis and Allied Conditions, ed. 6, Philadelphia, Lea & Febiger, 1960, p. 364.

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confusion and should therefore be banned. Every motor vehicle should carry a red reflector which can be erected and placed on the road at some distance behind the vehicle in case the vehicle has to stop on the side of the road for any reason.

Selection of persons deemed fit to hold a driver's licence should be the responsibility of the medical profession. Such selection must be based on a strict and complete examination of every applicant for a driver's licence: it must include a thorough investigation of the applicant's visual acuity (not only his ability to read test types, but also his ability to judge distance and speed), of both divisions of his eighth cranial nerve, of his heart (and if there is any suspicion of trouble an electrocardiogram should be taken), and of his central nervous system. If enquiry is positive regarding personal and/or family history of fits or epilepsy, or regarding personal history of intake of drugs and other substances such as insulin, an electroencephalogram should be taken. Certain persons with neuropathic and psychopathic personalities should be excluded from holding driving licences. It would be advisable to have examinations for driving licences repeated every 3 to 5 years.

If accidents must happen, then prevention of injuries becomes the major concern. Again, motor vehicle design and equipment is a most important factor. The first essential is a safety harness which should include shoulder supports and braces to prevent "whip-lash" injury, as well as the ordinary safety belt to prevent ejection from the vehicle: ejection from the vehicle accounts for 60% of all serious injuries, and for 80% of all deaths in traffic accidents. The next essential consists of some form of head protection, as a beret with a thin skull-cap of metal or of some other hard material. Alterations in the design of the vehicle itself should include: (1) a collapsible steering column, or perhaps no steering column at all (as in aircraft); (2) a well-padded dashboard without any projecting features, and padding on the back of the front seat; (3) adequate locks on all doors to prevent ejection; (4) a high back to the front seat, high enough to support the head and prevent "whip-lash" injury; (5) buffers for the front bumpers to absorb the shock of collision with an object or with a pedestrian; (6) narrow front pillars to allow for a full field of vision; and (7) no projecting knobs or fittings either on the inside or the outside of the vehicle.

When injuries have occurred, it is the doctor's role to prevent death and permanent disability. First aid, applied quickly and scientifically, as soon as possible after the accident, is the first step in the salvage of victims. In this regard, "traumatology", with the teaching and training, not only of first-aid men, ambulance attendants, and nurses, but also of young graduate doctors (who are usually the first to examine and treat accident cases), has become an important new life-saving specialty. As a corollary to this, modern and efficient methods of transportation must be provided; this involves the provision, not only of ambulances, but also of equip-

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ment in these vehicles capable of dealing with every type of emergency. Such adequately equipped ambulances make speeding, which may do further harm to the patient and/or cause another accident, entirely unnecessary. Frequent moving of the accident victim, which may cause him further injury, can be avoided by the use of special litters, such as the "Transaver" equipment or the "theatre canvas", from which a patient need not be removed until he is finally put to bed in the postoperative recovery room. Another essential is the provision of adequate accommodation and facilities at hospitals for the reception and immediate treatment, at any time of the day or night, of accident cases.

Injury, disability and death are costs too great to pay for extreme eye-catching styling and a little extra economy in automobiles. On the other hand, the cost of medical examinations to select persons fit to hold a driver's licence, and the cost of adequate and efficient care of accident victims beginning with first-aid and continuing until the patient is fit to resume his pre-accident occupation or some other form of employment, would be more than compensated by salvage of active working lives and by shortening of long periods of disablement.

POLYCYTHEMIA AND HYDRONEPHROSIS

A case of polycythemia associated with unilateral hydronephrosis was recently reported by Martt Sayman and Neal (*Ann. Int. Med.* 54: 790, 1961). This is the sixth instance of this combination reported in the medical literature.

A 62-year-old male presented with a hemoglobin of 23.5 g. per 100 c.c., a hematocrit of 71%, a mild leukocytosis, and splenomegaly. Hydronephrosis of the left kidney was discovered by x-ray studies of the genitourinary tract, and a left nephrectomy was performed. Before the operation, a cardiac catheter was moved up the inferior vena cava to the orifice of the left renal vein, and 400 c.c. of blood was collected for determination of erythropoietin activity. No erythropoietin was demonstrated in the sample. The polycythemia was corrected before surgery by repeated phlebotomies. Thirteen months after nephrectomy the hemogram was as follows: hemoglobin 15.0 g. per 100 c.c.; hematocrit 46%; leukocytes 14,800. The spleen was no longer palpable.

The mechanism by which polycythemia is produced as a complication of certain renal diseases—particularly renal carcinoma—is unknown. The theory that the involved kidney (or tumour) produces erythropoietin or an erythrocyte-stimulating factor is not supported by the examination of the renal-vein blood in this case. However, since submission of this paper for publication, erythropoietin has been isolated from the cyst wall and from fluid within the cyst in a patient with polycythemia and a large unilocular cyst of the kidney.

The disappearance of the polycythemia after removal of the affected kidney has also been reported by others, particularly in cases of renal carcinoma. Data exist in sufficient quantity to justify the recommendation of a meticulous urologic investigation in patients with polycythemia of obscure etiology.